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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants:	H. William BOSCH et al.
Title:	NOVEL GLIPIZIDE COMPOSITIONS
Appl. No.:	10/701,064
Filing Date:	11/05/2003
Examiner:	Susan T. TRAN
Art Unit:	1615
Confirmation No.	6295

AMENDED BRIEF ON APPEAL

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Sir:

Under the provisions of 37 C.F.R. § 41.37 and in response to the Notification of Non-Compliant Appeal Brief mailed on October 22, 2007 ("Notification"), Appellants submit this Amended Appeal Brief. The Notification stated that the Headings "Evidence Appendix" and "Related Proceedings Appendix" are missing. The present Amended Brief includes the Evidence Appendix and the Related Proceedings Appendix. Authorization is hereby given to charge any deficiency (or credit any balance) to the undersigned deposit account 19-0741 if any fees are due. Appellants hereby appeal the Advisory Action rejection of claims 1-15, 17-24, 36-75 and 87-90 in the above-identified application to the Board of Appeals and Interferences.

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REAL PARTY IN INTEREST

The real party of interest is Elan Pharma International Limited.

RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any related appeal or interferences.

STATUS OF CLAIMS

Claims 25-35 and 76-86 are cancelled and claims 1-24, 36-75 and 87-90 are pending in the application, with claims 1, 16, 40 and 58 being the independent claims. Claim 16 is allowed. Claims 1-15, 17-24, 36-75 and 87-90 are rejected and appealed. A copy of the pending claims is presented in the APPENDIX of this Brief.

STATUS OF AMENDMENTS

An amendment after the Final Rejection dated April 6, 2007, was filed on July 6, 2007, to comply with the Examiner's request to recite the percentage amount ranges of the glipizide and surface stabilizer in independent claims 1, 40 and 58. Claims 7-8, 49-50 and 64-65 were also amended to avoid redundancy. Further, the amendment after final amended claim 16 to be an independent claim, as requested by the Examiner, and cancelled claims 25-35 and 76-86. All amendments have been entered.

SUMMARY OF CLAIMED SUBJECT MATTER

The subject matter as claimed in each independent claim is presented below. The citation to the specification follows the procedure used in the Board's Standing Order for Patent Interferences, Paragraph 110.

Independent claim 1 reads as follows:

1. A composition comprising:

(a) particles of glipizide or a salt thereof {**page 22, lines 25-28**} having an effective average particle size of less than about 2000 nm {**page 29, lines 1-2 and lines 12-14**}; and

(b) at least one surface stabilizer {**page 6, lines 14-16**};

wherein the glipizide or a salt thereof is present in an amount of from about 99.5% to about 0.001%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients {**page 30. lines 6-9**}; and

wherein the at least one surface stabilizer is present in an amount of from about 0.5% to about 99.999% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients {**page 30, lines 10-13**}.

Claim 16 reads as follows:

16. A composition comprising:

(a) particles of glipizide or a salt thereof {**page 22, lines 25-28**}, wherein the glipizide particles have an effective average particle size of less than about 2000 nm {**page 29, lines 1-2 and lines 12-14**};

(b) at least one surface stabilizer {**page 6, lines 14-16**}; and

(c) at least one additional glipizide composition having an effective average particle size which is different from the effective average particle size of the glipizide particles of (a) {**page 19, lines 4-22**}.

Claim 40 reads as follows:

40. A method of making a glipizide composition comprising contacting particles of glipizide or a salt thereof with at least one surface stabilizer for a time and under conditions sufficient to provide a glipizide composition having an effective average particle size of less than about 2000 nm {**page 6, lines 23-25; page 29, lines 1-2 and lines 12-14**}

wherein the glipizide or a salt thereof is present in an amount of from about 99.5% to about 0.001%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients {**page 30. lines 6-9**}; and

wherein the at least one surface stabilizer is present in an amount of from about 0.5% to about 99.999% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients {**page 30, lines 10-13**}.

Claim 58 reads as follows:

58. A method of treating diabetes in a subject in need thereof {**page 6, lines 28-31**} comprising administering to the subject an effective amount of a composition {**page 32, lines 17-30**} comprising:

(a) particles of a glipizide or a salt thereof, wherein the glipizide particles have an effective average particle size of less than about 2000 nm { **page 32, lines 17-30; page 29, lines 1-2 and lines 12-14**}; and

(b) at least one surface stabilizer {**page 6, lines 14-16**},

wherein the glipizide or a salt thereof is present in an amount of from about 99.5% to about 0.001%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients {**page 30. lines 6-9**};

wherein the at least one surface stabilizer is present in an amount of from about 0.5% to about 99.999% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients {**page 30, lines 10-13**}.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellants present two grounds of rejection for consideration on appeal.[1]

Specifically, Appellants present for consideration the rejection of claims 1-8, 10-11, 13-15, 17-35, 40-43, 45-50, 52-53, 55-65, 67-68 and 70-90 under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,145,684 to Liversidge *et al.* ("Liversidge") in view of U.S. Patent No. 5,024,843 to Kuczynski *et al.* ("Kuczynski").

Further, Appellants present for consideration the rejection of claims 9, 12, 44, 51, 54, 66 and 69 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Liversidge in view of Kuczynski and international application WO 98/07414 to Parikh *et al.* ("Parikh").

[1] The Final Office Action dated April 6, 2007, also sets forth a Written Description rejection and an Enablement rejection of claims 25-35 and 76-86, and two provisional nonstatutory obviousness-type double patenting rejections of claims 1-15 and 17-57. Applicants canceled claims 25-35 and 76-86 in the Amendment and Reply filed on July 6, 2007, and submitted therewith Terminal Disclaimers. Accordingly, these rejections are moot.

GROUPING OF CLAIMS

Claims 1-15, 17-24, 36-75 and 87-90 stand and fall together.

SUMMARY OF THE ARGUMENTS

Claim 1 recites a composition comprising *glipizide particles having an effective average particle size of less than about 2000 nm*. Claim 40 recites a method of providing a *glipizide particle composition having an effective average particle size of less than about 2000 nm*. Claim 58 recites a method of treating diabetes in a subject comprising administering to the subject a composition comprising *glipizide particles having an effective average particle size of less than about 2000 nm*.

During prosecution, the Examiner alleged that Liversidge teaches particles of a crystalline drug and a surface modifier having an effective average particle size of less than 400 nm. Liversidge discloses anti-diabetic agents in the laundry list of drug substances that may be suitable for the invention. Applicants assert that Liversidge fails to suggest glipizide particles having an effective average particle size of less than about 2000 nm.

The Examiner recognized the deficiencies of Liversidge in failing to disclose glipizide. The Examiner relied on the disclosure of Kuczynski for the teachings that glipizide is an antidiabetic drug. The Examiner concluded that it would have been obvious to select glipizide as an anti-diabetic drug and formulate it into nanoparticles as claimed. Kuczynski, however, does not teach nanoparticulate glipizide compositions.

In essence, the Examiner applies an incorrect legal standard by persistently asserting that the disclosure of anti-diabetic agents in Liversidge renders obvious the use of any known anti-diabetic agent. To the contrary, the M.P.E.P. "Genus-Species Guidelines"[2] state that "the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness." The Examiner has not provided any compelling evidence to show *prima facie* obviousness in selecting glipizide among the vast number of anti-

[2] M.P.E.P., section 2144.08. *See* also *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) and *In re Deuel*, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995).

diabetic agents encompassed by the anti-diabetic agents genus disclosed by Liversidge, thereby to arrive at the claimed nanoparticulate glipizide composition.

Nevertheless, in the Advisory Action of July 23, 2007, the Examiner alleged that it would have been obvious to one of ordinary skill in the art to modify the nanoparticles of Liversidge using glipizide as an anti-diabetic agent, because Liversidge discloses anti-diabetic agents and Kuczynski teaches that glipizide is a well known anti-diabetic agent.

ARGUMENTS

A. The Rejection of Claims 1-8, 10-11, 13-15, 17-35, 40-43, 45-50, 52-53, 55-65, 67-68 and 70-90 under 35 U.S.C. § 103(a) over Liversidge in view of Kuczynski

The Supreme Court recently reaffirmed the Graham factors for determining obviousness.[3] The Graham factors, as outlined by the Supreme Court[4], are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the claimed invention and the prior art; 3) resolving the level of ordinary skill in the pertinent art; and 4) evaluating evidence of secondary consideration. The Supreme Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a), and held that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions. The Court noted that it is *"important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed.*

Appellants' claims are patentable over the combination of Liversidge and Kuczynski because there is no reason that would have prompted a person of ordinary skill in the relevant field to combine the elements now claimed in Appellants' invention. Appellants assert there is no reason to combine the element in the claimed fashion because (I) there is no predictive principle that all drugs may be formulated into nanoparticles; (II) the fact that a claimed species is encompassed by a genus disclosed in the prior art is not sufficient by itself to establish a *prima facie* case for obviousness; (III) the genus of anti-diabetic agents is enormous and each class of anti-diabetic agents has different properties and different mechanisms of action; (IV) *In re Spada*

[3] *KSR Int'l Co. v. Teleflex Inc.* (No. 04-1350) (U.S., April 30, 2007).

[4] *Graham et al. v. John Deere Co. of Kansas City et al.,* 383 U.S. 1 (1966).

cannot be applied because the class of compounds known as anti-diabetic agents do not possess identical compositions, and (V) the "obvious to try" standard may not be applied in the present application.

I. THERE IS NO PREDICTIVE PRINCIPLE THAT ALL DRUGS MAY BE FORMULATED INTO NANOPARTICLES

The art of formulating drugs into nanoparticles is highly unpredictable. The Examiner's conclusion of obviousness relies upon the inference that formulating nanoparticles of anti-diabetic agents is routine. The Examiner has, however, failed to prove that there is a predictive principle that all anti-diabetic drugs may be formulated into nanoparticles. To the contrary, there is evidence in the cited prior art that formulating drugs into nanoparticles, not just anti-diabetic agents, is highly unpredictable. Comparative examples A-F in Liversidge clearly demonstrate that not all combinations of drugs and surface stabilizers produce nanoparticulates. Rather, some of the drugs flocculate or aggregate into large particles.

Thus informed, the artisan skilled in the art would not have known *a priori* whether glipizide can be formulated into nanoparticles, particularly given the comparative examples in Liversidge. Since the prior art fails to teach that glipizide can be formulated into nanoparticles, the reasonably creative person skilled in the art would have had no ground to create from and would not have found it obvious to prepare glipizide nanoparticles. At least for this reason, the Examiner's rejection should be reversed in whole.

II. THE FACT THAT A CLAIMED SPECIES IS ENCOMPASSED BY A GENUS DISCLOSED IN THE PRIOR ART IS NOT SUFFICIENT BY ITSELF TO ESTABLISH A PRIMA FACIE CASE OF OBVIOUSNESS

The Federal Circuit has clarified the law regarding a *prima facie* case of obviousness in a genus-species situation. Specifically, the court held that "*The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a prima facie case of obviousness*".[2]

The M.P.E.P[5] sets forth the following criteria in order to determine whether there is a *prima facie* case of obviousness when a prior art reference discloses a genus: (a) the structure of the disclosed prior art genus and that of any expressly described species or subgenus within the genus; (b) any physical or chemical properties and utilities disclosed for the genus, as well as any suggested limitations on the usefulness of the genus, and any problems alleged to be addressed by the genus; (c) the predictability of the technology; and (d) the number of species encompassed by the genus taking into consideration all of the variables possible.

(a) Structural Differences

"Some teaching of a structural similarity will be necessary to suggest selection of the claimed species or subgenus". As indicated above, since anti-diabetic agents are very different in their chemical structure and physical properties, one of ordinary skill in the art would have not been motivated, in view of the disclosure of Liversidge, to select glipizide among the myriad of available anti-diabetic agents.

(b) Different Properties

As demonstrated above, each class of anti-diabetic agents has different properties. Therefore, the artisan of ordinary skill in the art would have no reason to favor one particular class of anti-diabetic agents over another or one particular anti-diabetic agent over another.

(c) Unpredictable Technology

As stated above, there is no predictive principle that all drugs may be formulated into nanoparticles, and the Examiner has failed to prove that the art of making nanoparticles with any drug is a predictable technology. To the contrary, the reference cited by the Examiner against Appellants' invention, Liversidge, clearly demonstrates that not all combinations of drugs and surface stabilizers produce nanoparticulates after milling. Rather, some of the drugs flocculate or aggregate into large particles (*see* Comparative Examples A-F).

[5] M.P.E.P., section 2144.08A

Furthermore, because of the large variability in chemical structure and physical properties of anti-diabetic agents, the artisan skilled in the art would not have known *a priori* whether every anti-diabetic agent can be formulated into nanoparticles. Thus, the artisan skilled in the art would not have found it obvious to prepare glipizide nanoparticles. These factors clearly weigh against a conclusion of a *prima facie* case of obviousness.

(d) The Immensity of the Genus

As demonstrated above, anti-diabetic agents are an immense group of drugs and chemical compounds that differ in their chemical structure, physical properties, therapeutic effects and adverse reactions. Anti-diabetic agents do not constitute a small recognizable class of compounds with common properties. Thus, the mere disclosure of the genus of anti-diabetic agents in the primary reference does not render obvious each and every anti-diabetic agent.

III. THE GENUS OF ANTI-DIABETIC AGENTS IS ENORMOUS AND EACH CLASS OF ANTI-DIABETIC AGENTS HAS DIFFERENT PROPERTIES AND DIFFERENT MECHANISMS OF ACTION

The Board is urged to consider the totality of the record to the extent sufficient to satisfy itself. Appellants surveyed the anti-diabetic agents' literature and identified a great number of publications that amply illustrate the state of the art before Appellants' invention. The references listed below clearly show that an overwhelming number of anti-diabetic agents was available before Appellants' invention and demonstrates that each class of anti-diabetic agents has a different mechanism of action and relative advantages and disadvantages:

Koski, RR "Practical Review of Oral Antihyperglycemic Agents for Type 2 Diabetes Mellitus" *American Association of Diabetes Educators*, Published by SAGE Publications (2006), attached as Exhibit A.

Wagman, AS and Nuss, JM "Current Therapies and Emerging Targets for the Treatment of Diabetes" *Current Pharmaceutical Design 7*: 417-50 (2001), attached as Exhibit B.

Inzucchi, SE "Oral Antihyperglycemic Therapy for Type 2 Diabetes" *JAMA 287 (3)*: 360-372 (2002), attached as Exhibit C.

DeWitt, DE and Hirsch, IB "Outpatient Insulin Therapy in Type 1 and Type 2 Diabetes Mellitus", *JAMA 289 (17)*: 2254-2264 (2003), attached as Exhibit D.

Zhou, YP and Grill, VE "Long-Term Exposure of Rat Pancreatic Islets to Fatty Acids Inhibits Glucose-Induced Insulin Secretion and Biosynthesis through a Glucose Fatty Acid Cycle" *J. Clin. Invest. 93*: 870-876 (1994), attached as Exhibit E.

U.S. Patent No. 5,972,881, attached as Exhibit F.

U.S. Patent No. 5,998,463, attached as Exhibit G.

The genus of anti-diabetic agents includes, among others, biguanides, such as metformin and phenformin; glucosidase inhibitors, such as precose, acarbose, miglitol, emiglitate, voglibose and camiglibose; insulins, insulin analogues and insulin secretagogues; meglitinides, such as nateglinide, repaglinide and mitiglinide; sulfonylureas, such as acetohexamide, chlorpropamide, gliclazide, glibenclamide, glimepiride, glipizide, glyburide, tolazamide and tolbutamide; biguanide/glyburide combinations, such as Glucovance®™; thiazolidinediones, such as troglitazone, rosiglitazone and pioglitazone; PPAR-alpha agonists; PPAR alpha/gamma dual agonists; glycogen phosphorylase inhibitors; RXR agonists; imidazolines; fatty acid oxidation inhibitors; inhibitors of fatty acid binding protein (aP2); and SGLT2 inhibitors.

People affected by Type 2 diabetes Mellitus have insulin resistance, impaired insulin secretion and/or increased hepatic glucose production. Diet, exercise, anti-diabetic medications and insulin are the available therapies for the treatment of patients suffering from Type 2 Diabetes Mellitus. Anti-diabetic agents are used in people who fail to meet the glycemic goals with diet and exercise. Insulin and insulin analogues are used when oral therapy fails or is not well tolerated by the patient. Since each class of anti-diabetic agents has its unique mechanism

of action, adverse effects and prescribing precautions, pharmacologic therapy is tailored to the goals and needs of each individual patient. Thus, when selecting an anti-diabetic agent for treatment, the effects on glucose and lipids, adverse reaction profile and route of elimination must be considered prior to administration to the patient.

Following is a description of few of the many classes of anti-diabetic agents that were available before Appellants' invention. Each class includes compounds that differ in their chemical structure and physical properties, such that each class of anti-diabetic agents has its unique mechanism of action and relative advantages and disadvantages.

a) Metformin is the only biguanide FDA-approved for use in the United States. Metformin is an insulin sensitizer, as it acts by decreasing hepatic glucose production and glucose absorption in the presence of insulin, and by increasing glucose uptake into skeletal muscle. Metformin is a very attractive option for patients, as it decreases triglyceride concentrations, LDL cholesterol, total cholesterol and body weight, and increases HDL cholesterol. Additionally, metformin does not affect insulin secretion, so it does not cause hypoglycemia. Metformin, however, should be used with caution in the elderly, in patients with congestive heart failure and in patients with acute conditions predisposing them to acute renal failure or acidosis. Additionally, metformin is contraindicated in 1) patients with high level of serum creatinine; 2) patients with hepatic dysfunction; 3) patients with congestive heart failure requiring pharmacologic treatment; 4) patients with a history of drinking; and 5) patients with acute or chronic lactic acidosis. Side effects, especially gastrointestinal disturbances, and asymptomatic subnormal B12 levels, are common.

b) Alpha-glucosidase inhibitors include acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose and MDL-73,945. Acarbose (Precose®) and miglitol (Glyset®) are FDA-approved for use in the United States. Alpha-glucosidase inhibitors block the action of alpha-glucosidase enzymes at the brush border of the intestine. The inhibition slows the breakdown of dietary oligosaccharides and disaccharides and the subsequent delayed digestion of

carbohydrates decreases post-prandial glucose concentrations. Although alpha-glucosidase inhibitors are less efficient than other drugs, these agents are attractive because they have minimal effect on cholesterol and body weight. Flatulence and gastrointestinal pain are common side effects in patients taking alpha-glucosidase inhibitors. In addition, acarbose may cause elevations in liver function tests. Miglitol is excreted primarily by the kidneys and should be used with caution in moderate to severe renal failure.

c) Insulin products include: 1) rapid-acting insulins, such as Lispro and Aspart, which are rapidly absorbed; 2) short-acting or regular insulin, which acts almost immediately when injected intravenously; 3)intermediate-acting insulin, such as neutral protamine Lispro (insulin lispro protamine, NPL), protamine crystalline aspart, neutral protamine Hagedorn (isophane insulin, NPH), which is slowly adsorbed due to the addition of protamine to regular insulin, and Lente insulin, which is regular insulin bound to zinc and has a slightly longer effective duration than NPH; 4) long-acting insulin, such as the slowly-adsorbed Ultralente insulin (insulin zinc extended) and the extended release insulin glargine. The major and most common adverse effects of insulin therapy are hypoglycemia and weight gain. Rate of absorption and onset and duration of action are the most variable factors among the different types of insulin available, and adjustments in the regimen, dosage and type or types of insulin administered to the patient are often necessary to correct hypoglycemia.

d) Insulin secretagogues include linogliride, insulinotropin, exendin-4 (Exenatide), BTS-67582 and A-4166.

e) Repaglinide (Prandin®) and nateglinide (Starlix®) are FDA-approved meglitinides for use in the United States. Because of their rapid onset, meglitinides stimulate pancreatic insulin secretion immediately after meal ingestion and thus attenuate post-prandial glucose excursions. Because of their short duration of action, the incidence of hypoglycemia associated with meglitinides is reduced. However, meglitinides need to be administered

frequently, may increase body weight and should not be administered to patients with impaired liver or kidney function, because they are hepatically metabolized and renally cleared.

f) Sulfonylureas lower blood sugar by binding to the sulfonylurea receptor on the membrane of beta cells in the pancreas. They facilitate calcium transport into the cells and increase endogenous insulin secretion. These compounds may be used only in patients with viable β-cells. Sulfonylureas have no effect on triglycerides or cholesterol and most of them undergo renal elimination. There is some evidence that sulfonylureas also sensitize β-cells to glucose, limit glucose production in the liver, decrease lipolysis and decrease release of insulin from the liver. Various sulfonylureas have different pharmacokinetics. Second generation sulfonylureas (glipizide, glyburide and glimepiride) have increased potency by weight, compared to first-generation sulfonylureas (acetohexamide, chlorpropamide, tolazamide and tolbutamide), but have essentially equal efficacy and are more expensive. Side effects of sulfonylureas include hypoglycemia, weight gain, dermatological and hematological reactions and gastrointestinal disturbances. The choice depends on the propensity of the patient to develop hypoglycemia.

g) Glucovance® is a fixed combination of glyburide and metformin. Combination therapies involving two or three drug classes having distinct mechanisms of action, such as sulfonylurea and metformin, metformin and thiazolidinediones and sulfonylurea and thiazolidinediones, improve glycemic control, decrease overall drug dosing and thus minimize side effects.

h) Thiazolidinediones include ciglitazone, troglitazone, rosiglitazone (Avandia®), pioglitazone (Actos®), englitazone and darglitazone. Thiazolidinediones act by stimulating the peroxisome proliferative-insulin-activated receptor gamma (PPAR) that increases insulin-stimulated glucose uptake in skeletal muscle cells and adipose tissue, and by inhibiting hepatic gluconeogenesis. When used as monotherapy, both rosiglitazone and pioglitazone do not cause hypoglycemia and raise HDL cholesterol. However, thiazolidinediones are associated with weight gain and may cause an increase in plasma volume that results in edema, and small

decreases in hemoglobin and hematocrit. Rosiglitazone and pioglitazone should be used with caution in patients with advanced congestive heart failure.

i) PPAR alpha agonists, which include bezafibrate, clofibrate, gemfibrozil, fenofibrate, ciprofibrate, and bezafibrate, reduce glucose-induced insulin secretion, lower plasma triglycerides and cholesterol levels, elevate the level of plasma HDL cholesterol and are beneficial in the prevention of ischemic heart disease in individuals with dyslipidemia.

j) Dual PPAR alpha/gamma agonists are compounds that exhibit both significant PPAR alpha and PPAR gamma agonism. These compounds include dihydrocinnamate and cinnamate derivatives, L-tyrosine derivatives, phenyl propanoic acid and propanoic acid derivatives, isoxazolidinedione and oxazolidinedione derivatives, thiazolidinediones, tricyclics, carboxylic acid and malonic acid derivatives, oxobenzylglycine derivatives, fibrates, quinoline derivatives, alkanoate derivatives, phenyalkyloxy phenyl derivatives, benzamide derivatives and isoprenols.

k) Angiotensin II Type I receptor (A-2) antagonists decrease vasoconstriction associated with hyperlipidemia, dyslipidemia and hyperglycemia. A-2 antagonists include abitesartan, benzyllosartan, elisartan, embusartan, enoltasosartan, fonsartan, forasartan, glycyllosartan, milfasartan, olmesartan, opomisartan, pratosartan, ripisartan, eprosartan, candesartan, irbesartan, saprisartan, tasosartan, telmisartan, valsartan, zolasartan and losartan.

l) RXR agonists, which include the compounds JTT-501, MCC-555, MX-6054, DRF2593,GI-262570, KRP-297 and LG100268, mimic or enhance the antidiabetic effects of thiazolidinedione compounds. RXR agonists are insulin sensitizers that increase insulin-stimulated glucose uptake, lower the level of triglyceride, suppress the level of insulin and increase the level of HDL cholesterol.

m) Imidazolines, such as midaglizole, isaglidole, deriglidole, idazoxan, efaroxan and fluparoxan, are potent stimulators of insulin secretion in pancreatic β-cells.

n) Fatty acid oxidation inhibitors, such as clomoxir and etomoxir; improve fasting hyperglycemia and hypertriglyceridemia.

Additional anti-diabetic agents include beta.-agonists, such as BRL 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243, TAK-667, AZ40140; phosphodiesterase inhibitors, such as sildenafil, L686398 and L-386,398; lipid-lowering agents, such as benfluorex and atorvastatin; anti-obesity agents, such as fenfluramine, orlistat and sibutramine; vanadate and vanadium complexes, such as Naglivan®™, and peroxovanadium complexes; amylin and amylin derivatives, such as pramlintide and AC-137; lipoxygenase inhibitors, such as masoprocal; somatostatin analogs, such as BM-23014, seglitide, octreotide; glucagon antagonists, such as BAY 276-9955; insulin signaling agonists; insulin mimetics; PTP1B inhibitors, such as L-783281, TER17411 and TER17529; gluconeogenesis inhibitors, such as GP3034; antilipolytic agents, such as nicotinic acid, acipimox and WAG 994; glucose transport stimulating agents, such as BM-130795; glucose synthase kinase inhibitors, such as lithium chloride, CT98014 and CT98023; galanin receptor agonists; MTP inhibitors; growth hormone secretagogues; NPY antagonists, such as PD-160170, BW-383, BW1229, CGP-71683A, NGD 95-1 and L-152804; anorectic agents, including 5-HT and 5-HT2C receptor antagonists and/or mimetics, such as dexfenfluramine, Prozac®™, Zoloft®™; CCK receptor agonists, such as SR-27897B; galanin receptor antagonists; MCR-4 antagonists, such as HP-228; leptin; 11-beta-hydroxysteroid dehydrogenase type-I inhibitors; urocortin mimetics; CRF antagonists and CRF binding proteins, such as RU-486 and urocortin.

It is beyond question that the genus of anti-diabetic agents is enormous, and each class of anti-diabetic agents has a different mechanism of action and relative advantages and disadvantages. Therefore, as one of ordinary skill in the art would have appreciated, there is no gripping reason to favor one particular class of anti-diabetic agents over another or one particular anti-diabetic agent over another.

Because the Examiner has never acknowledged the enormity of the genus of anti-diabetic agents, and the M.P.E.P. mandates that the size of the genus be considered as a factor in determining the obviousness of a species, reversal in whole of the obviousness rejection is warranted on this ground.

IV. IN RE SPADA CANNOT BE APPLIED BECAUSE ANTI-DIABETIC AGENTS ARE NOT PRODUCTS OF IDENTICAL COMPOSITION

The Federal circuit's decision for *In re Spada*[6] was based on pressure sensitive adhesives that were created by using polymers of the same monomers in overlapping ratios as disclosed in the prior art. The final polymer product of the reference was different from the product disclosed in the prior art. The Court found that "the virtual identity of monomers and procedures sufficed to support a *prima facie* case of unpatentability of Spada's polymer latexes for lack of novelty." The *In re Spada* decision, however, cannot be applied in the present case, because anti-diabetic agents are <u>**not**</u> a small group of products having identical chemical structure and properties. Rather, as indicated above, anti-diabetic agents are an immense group of drugs and chemical compounds that differ in their chemical structure and physical properties, such that each class of anti-diabetic agents has its unique mechanism of action. Therefore, the principle that "Products of identical chemical composition can not have mutually exclusive properties" may not be invoked.

V. THE "OBVIOUS TO TRY" STANDARD MAY NOT BE APPLIED IN THE PRESENT APPLICATION

The Examiner's presumption that it would be obvious to select glipizide as an anti-diabetic agent in view of the disclosure of the prior art relies, at best, on the "obvious to try" standard .

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[6] *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

"*When the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them...*", "*anticipation can only be found if the classes of substituents are sufficiently limited or well delineated*"[7].

Furthermore, "*when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.*"[3]

The genus of anti-diabetic agents **is not** a limited group of compounds, and **does not** present a small, finite number of predictable solutions. The selection of an anti-diabetic agent for nanoparticulate formulations requires knowledge in the specific technical field of nanoparticulate technology that the selected anti-diabetic agent can be formulated into nanoparticles. It is therefore evident that the "obvious to try" standard may not be applied in the present application because there is an immense number of known anti-diabetic agents available, and since the nanoparticulate technology is so unpredictable, it would be time-consuming and cost-inefficient for the artisan skilled in the art to determine which anti-diabetic agent can be formulated into nanoparticles and which anti-diabetic agent cannot. Therefore, the person of ordinary skill in the art would have no reason to select glipizide among the myriad of available anti-diabetic agents.

VI. CONCLUSION

Independent claims 1, 40 and 58 recite a composition and methods comprising glipizide particles having an effective average particle size of less than about 2000 nm. The cited prior art fails to teach or suggest glipizide particles having an effective average particle size of less than about 2000 nm. Because of the lack of predictability in formulating drugs into nanoparticles and because of the multiplicity and variety in structure, properties, mechanism of action, therapeutic effects and adverse effects of the drugs, compounds and agents encompassed by the genus of anti-diabetic agents, the artisan skilled in the art would not have known *a priori* whether every anti-diabetic agent can be formulated into nanoparticles and would have had no compelling

[7] *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990).

reason to select glipizide. The claimed invention is therefore non-obvious over the cited prior art. For at least these reasons, it is submitted that the invention of claims 1, 40 and 58, and depending claims 2-8, 10-11, 13-15, 17-24, 41-43, 45-50, 52-53, 55-57, 59-65, 67-68, 70-75 and 87-90 is patentable.

B. The Rejection of Claims 9, 12, 44, 51, 54, 66 and 69 under 35 U.S.C. § 103(a) over Liversidge in view of Kuczynski and Parikh

Parikh in combination with Liversidge and Kuczynski does not obviate the claimed invention because Parikh remedies none of the deficiencies of Liversidge and Kuczynski. Rather, the disclosure of Parikh is directed to compositions comprising microparticles of water-insoluble drugs prepared using a combination of one or more surface modifiers with a phospholipid. Parikh fails to teach or disclose glipizide, let alone nanoparticulate glipizide compositions.

In the Advisory Action, the Examiner stated that Parikh is relied upon for teaching the use of mixtures of surface modifiers, alleging that nanoparticulate glipizide is taught in Liversidge in view of Kuczynski.

But Liversidge in view of Kuczynski do not teach nanoparticulate glipizide compositions, as clearly demonstrated above. Therefore, no permutations of teachings from Liversidge and Kuczynski, with or without those of Parikh, could have suggested the invention of appealed claims 9, 12, 44, 51, 54, 66 and 69. Accordingly, the obviousness rejection should be reversed in whole.

CLAIM APPENDIX

1. (Previously Presented) A composition comprising:

(a) particles of glipizide or a salt thereof, wherein the glipizide particles have an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer;

wherein the glipizide or a salt thereof is present in an amount of from about 99.5% to about 0.001%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients; and
wherein the at least one surface stabilizer is present in an amount of from about 0.5% to about 99.999% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

2. (Original) The composition of claim 1, wherein the glipizide is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

3. (Original) The composition of claim 1, wherein the effective average particle size of the glipizide particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

4. (Previously Presented) The composition of claim 1, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

5. (Original) The composition of claim 1 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

6. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

7. (Previously Presented) The composition of claim 1, wherein the glipizide or a salt thereof is present in an amount selected from the group consisting of from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

8. (Previously Presented) The composition of claim 1, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

9. (Original) The composition of claim 1, comprising at least two surface stabilizers.

10. (Original) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

11. (Original) The composition of claim 10, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl -D-glucopyranoside; n-decyl -D-maltopyranoside; n-dodecyl -D-glucopyranoside; n-dodecyl -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl--D-glucopyranoside; n-heptyl -D-thioglucoside; n-hexyl -D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl--D-glucopyranoside; octyl -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

12. (Original) The composition of claim 10, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

13. (Previously Presented) The composition of claim 10, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-

dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylammonium bromide,

choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

14. (Original) The composition of any of claims 10, 12, or 13, wherein the composition is bioadhesive.

15. (Original) The composition of claim 1, comprising as a surface stabilizer hydroxypropyl cellulose.

16. (Previously Presented) A composition comprising:

(a) particles of glipizide or a salt thereof, wherein the glipizide particles have an effective average particle size of less than about 2000 nm;

(b) at least one surface stabilizer, and

(c) at least one additional glipizide composition having an effective average particle size which is different from the effective average particle size of the glipizide particles of (a).

17. (Original) The composition of claim 1, additionally comprising one or more non-glipizide active agents.

18. (Original) The composition of claim 17, wherein said additionally one or more non-glipizide active agents are selected from the group consisting of nutraceuticals, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics,

sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, parathyroid biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

19. (Original) The composition of claim 17, wherein said additionally one or more non-glipizide active agents are selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

20. (Original) The composition of claim 1, wherein upon administration to a mammal the glipizide particles redisperse such that the particles have an effective average particle size of less than about 2 microns.

21. (Original) The composition of claim 20, wherein upon administration the composition redisperses such that the glipizide particles have an effective average particle size

selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

22. (Original) The composition of claim 1, wherein the composition redisperses in a biorelevant media such that the glipizide particles have an effective average particle size of less than about 2 microns.

23. (Original) The composition of claim 22, wherein the biorelevant media is selected from the group consisting of water, aqueous electrolyte solutions, aqueous solutions of a salt, aqueous solutions of an acid, aqueous solutions of a base, and combinations thereof.

24. (Original) The composition of claim 22, wherein the composition redisperses in a biorelevant media such that the glipizide particles have an effective average particle size selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

25.-35. (Cancelled)

36. (Original) The composition of claim 1 formulated into a liquid dosage form, wherein the dosage form has a viscosity of less than about 2000 mPa·s, measured at 20C, at a shear rate of 0.1 (1/s).

37. (Original) The composition of claim 36, having a viscosity at a shear rate of 0.1 (1/s), measured at 20C, selected from the group consisting of from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

38. (Original) The composition of claim 36, wherein the viscosity of the dosage form is selected from the group consisting of less than about 1/200, less than about 1/100, less than about 1/50, less than about 1/25, and less than about 1/10 of the viscosity of a liquid dosage form of a non-nanoparticulate composition of glipizide, at about the same concentration per ml of glipizide.

39. (Original) The composition of claim 36, wherein the viscosity of the dosage form is selected from the group consisting of less than about 5%, less than about 10%, less than about 15%, less than about 20%, less than about 25%, less than about 30%, less than about 35%, less

than about 40%, less than about 45%, less than about 50%, less than about 55%, less than about 60%, less than about 65%, less than about 70%, less than about 75%, less than about 80%, less than about 85%, and less than about 90% of the viscosity of a liquid dosage form of a non-nanoparticulate composition of the glipizide, at about the same concentration per ml of glipizide.

40. (Previously Presented) A method of making a glipizide composition comprising contacting particles of glipizide or a salt thereof with at least one surface stabilizer for a time and under conditions sufficient to provide a glipizide composition having an effective average particle size of less than about 2000 nm;

wherein the glipizide or a salt thereof is present in an amount of from about 99.5% to about 0.001%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients; and

wherein the at least one surface stabilizer is present in an amount of from about 0.5% to about 99.999% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

41. (Original) The method of claim 40, wherein said contacting comprises grinding.

42. (Original) The method of claim 41, wherein said grinding comprises wet grinding.

43. (Original) The method of claim 40, wherein said contacting comprises homogenizing.

44. (Previously Presented) The method of claim 40, wherein said contacting comprises:

(a) dissolving the particles of a glipizide or a salt thereof in a solvent;

(b) adding the resulting glipizide solution to a solution comprising at least one surface stabilizer; and

(c) precipitating the solubilized glipizide having at least one surface stabilizer adsorbed on the surface thereof by the addition thereto of a non-solvent.

45. (Original) The method of claim 40, wherein the glipizide or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

46. (Original) The method of claim 40, wherein the effective average particle size of the glipizide particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1000 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

47. (Previously Presented) The method of claim 40, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

48. (Original) The method of claim 40, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

49. (Previously Presented) The method of claim 40, wherein the glipizide or a salt thereof is present in an amount selected from the group consisting of from about 95% to about 0.1%~~,~~ and from about 90% to about 0.5%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

50. (Previously Presented) The method of claim 40, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 5.0% to about 99.9%~~,~~ and from about 10% to about 99.5% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

51. (Original) The method of claim 40, utilizing at least two surface stabilizers.

52. (Original) The method of claim 40, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

53. (Original) The method of claim 52, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl -D-glucopyranoside; n-decyl -D-maltopyranoside; n-dodecyl -D-glucopyranoside; n-dodecyl -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl--D-glucopyranoside; n-heptyl -D-thioglucoside; n-hexyl -D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl--D-

glucopyranoside; octyl -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

54. (Original) The method of claim 52, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

55. (Previously Presented) The method of claim 52, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-

didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

56. (Original) The method of any of claims 52, 54, or 55, wherein the composition is bioadhesive.

57. (Original) The method of claim 40, utilizing hydroxypropylcellulose as a surface stabilizer.

58. (Previously Presented) A method of treating diabetes in a subject in need thereof comprising administering to the subject an effective amount of a composition comprising:

(a) particles of a glipizide or a salt thereof, wherein the glipizide particles have an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer,

wherein the glipizide or a salt thereof is present in an amount of from about 99.5% to about 0.001%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients;
wherein the at least one surface stabilizer is present in an amount of from about 0.5% to about 99.999% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

59. (Original) The method of claim 58, wherein the glipizide or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

60. (Original) The method of claim 58, wherein the effective average particle size of the glipizide particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

61. (Previously Presented) The method of claim 58, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

62. (Original) The method of claim 58, wherein the composition is a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized

formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

63. (Original) The method of claim 58, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

64. (Previously Presented) The method of claim 58, wherein the glipizide or a salt thereof is present in an amount selected from the group consisting of from about 95% to about 0.1% and from about 90% to about 0.5%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

65. (Previously Presented) The method of claim 58, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 5.0% to about 99.9%~~,~~ and from about 10% to about 99.5% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

66. (Original) The method of claim 58, utilizing at least two surface stabilizers.

67. (Original) The method of claim 58, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

68. (Original) The method of claim 67, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate,

noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl -D-glucopyranoside; n-decyl -D-maltopyranoside; n-dodecyl -D-glucopyranoside; n-dodecyl -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl--D-glucopyranoside; n-heptyl -D-thioglucoside; n-hexyl -D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl--D-glucopyranoside; octyl -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

69. (Original) The method of claim 67, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

70. (Previously Presented) The method of claim 67, wherein the surface stabilizer is selected from the group consisting of benzalkonium chloride, polymethylmethacrylate trimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, cationic lipids, sulfonium compounds, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl

dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

71. (Original) The method of any of claims 67, 69, or 70, wherein the composition is bioadhesive.

72. (Original) The method of claim 58, utilizing hydroxypropylcellulose as a surface stabilizer.

73. (Original) The method of claim 58, additionally comprising administering one or more non-glipizide active agents.

74. (Original) The method of claim 73, wherein said additionally one or more non-glipizide active agents are selected from the group consisting of nutraceuticals, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, parathyroid biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

75. (Original) The method of claim 73, wherein said additionally one or more non-glipizide active agents are selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam,

thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

76.-86. (Cancelled)

87. (Original) The method of claim 58, wherein the subject is a human.

88. (Original) The method of claim 58, wherein the method is used to treat indications where blood-glucose lowering drugs are typically used.

89. (Original) The method of claim 58, wherein the method is used to treat diabetes.

90. (Previously Presented) The method of claim 89, wherein the diabetes is non-insulin dependent diabetes mellitus.

EVIDENCE APPENDIX

Appellants append copies of the following references that were cited by the Examiner in the Office Action dated November 1, 2006:

U.S. Patent No. 5,145,684 to Liversidge *et al.*

U.S. Patent No. 5,024,843 to Kuczynski *et al.*

International Application WO 98/07414 to Parikh *et al.*

The following Exhibits were submitted with the Appeal Brief filed on October 2, 2007:

Exhibit A: Koski, RR "Practical Review of Oral Antihyperglycemic Agents for Type 2 Diabetes Mellitus" *American Association of Diabetes Educators*, Published by SAGE Publications (2006).

Exhibit B: Wagman, AS and Nuss, JM "Current Therapies and Emerging Targets for the Treatment of Diabetes" *Current Pharmaceutical Design 7*: 417-50 (2001).

Exhibit C: Inzucchi, SE "Oral Antihyperglycemic Therapy for Type 2 Diabetes" *JAMA 287 (3)*: 360-372 (2002).

Exhibit D: DeWitt, DE and Hirsch, IB "Outpatient Insulin Therapy in Type 1 and Type 2 Diabetes Mellitus", *JAMA 289 (17)*: 2254-2264 (2003).

Exhibit E: Zhou, YP and Grill, VE "Long-Term Exposure of Rat Pancreatic Islets to Fatty Acids Inhibits Glucose-Induced Insulin Secretion and Biosynthesis through a Glucose Fatty Acid Cycle" *J. Clin. Invest. 93*: 870-876 (1994).

Exhibit F: U.S. Patent No. 5,972,881.

Exhibit G: U.S. Patent No. 5,998,463.

RELATED PROCEEDINGS APPENDIX

None.

CONCLUSION

Appellants respectfully solicit the Honorable Board of Patent Appeals and Interferences to reverse the rejections of record and pass the application on to allowance.

Respectfully submitted,

Date Oct 31, 2007

By [signature]

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EVIDENCE APPENDIX

US005145684A

United States Patent [19]

Liverside et al.

[11] Patent Number: 5,145,684

[45] Date of Patent: Sep. 8, 1992

[54] SURFACE MODIFIED DRUG NANOPARTICLES

[75] Inventors: Gary G. Liversidge, West Chester; Kenneth C. Cundy, Pottstown, both of Pa.; John F. Bishop, Rochester; David A. Czekai, Honeoye Falls, both of N.Y.

[73] Assignee: Sterling Drug Inc., New York, N.Y.

[21] Appl. No.: 647,105

[22] Filed: Jan. 25, 1991

[51] Int. Cl.[5] A61K 9/14

[52] U.S. Cl. 424/489; 424/495; 424/499

[58] Field of Search 424/495, 489, 499

[56] References Cited

U.S. PATENT DOCUMENTS

2,671,750	3/1954	Macek	514/179
4,107,288	8/1978	Oppenheim	424/499
4,540,602	9/1985	Motoyama	424/495
4,826,689	5/1989	Violanto	424/489
4,851,421	7/1989	Iwasaki et al.	514/352

FOREIGN PATENT DOCUMENTS

411629	2/1991	European Pat. Off. .
2282330	11/1990	Japan .
2185397	7/1987	United Kingdom .
2200048	7/1988	United Kingdom .

OTHER PUBLICATIONS

Lachman et al., "the Theory and Practice of Industrial Pharmacy", Chapter 2, Milling (1986).

Remington's Pharmaceutical Sciences 17th Edition, Chapter 20, Schott, H., "Colloidal Dispersions".

Primary Examiner—Thurman K. Page
Assistant Examiner—William E. Benston, Jr.
Attorney, Agent, or Firm—Arthur H. Rosenstein; William J. Davis

[57] ABSTRACT

Dispersible particles consisting essentially of a crystalline drug substance having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm, methods for the preparation of such particles and dispersions containing the particles. Pharmaceutical compositions containing the particles exhibit unexpected bioavailability and are useful in methods of treating mammals.

20 Claims, No Drawings

SURFACE MODIFIED DRUG NANOPARTICLES

FIELD OF THE INVENTION

This invention relates to drug particles, methods for the preparation thereof and dispersions containing the particles. This invention further relates to the use of such particles in pharmaceutical compositions and methods of treating mammals.

BACKGROUND OF THE INVENTION

Bioavailability is the degree to which a drug becomes available to the target tissue after administration. Many factors can affect bioavailability including the dosage form and various properties, e.g., dissolution rate of the drug. Poor bioavailability is a significant problem encountered in the development of pharmaceutical compositions, particularly those containing an active ingredient that is poorly soluble in water. Poorly water soluble drugs, i.e., those having a solubility less than about 10 mg/ml, tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation. Moreover, poorly water soluble drugs tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with fully soluble drug substances.

It is known that the rate of dissolution of a particulate drug can increase with increasing surface area, i.e., decreasing particle size. Consequently, methods of making finely divided drugs have been studied and efforts have been made to control the size and size range of drug particles in pharmaceutical compositions. For example, dry milling techniques have been used to reduce particle size and hence influence drug absorption. However, in conventional dry milling, as discussed by Lachman, et al., *The Theory and Practice of Industrial Pharmacy*, Chapter 2, "Milling", p. 45, (1986), the limit of fineness is reached in the region of 100 microns (100,000 nm) when material cakes on the milling chamber. Lachman, et al. note that wet grinding is beneficial in further reducing particle size, but that flocculation restricts the lower particle size limit to approximately 10 microns (10,000 nm). However, there tends to be a bias in the pharmaceutical art against wet milling due to concerns associated with contamination. Commercial airjet milling techniques have provided particles ranging in average particle size from as low as about 1 to 50 μm (1,000–50,000 nm).

Other techniques for preparing pharmaceutical compositions include loading drugs into liposomes or polymers, e.g., during emulsion polymerization. However, such techniques have problems and limitations. For example, a lipid soluble drug is often required in preparing suitable liposomes. Further, unacceptably large amounts of the liposome or polymer are often required to prepare unit drug doses. Further still, techniques for preparing such pharmaceutical compositions tend to be complex. A principal technical difficulty encountered with emulsion polymerization is the removal of contaminants, such as unreacted monomer or initiator, which can be toxic, at the end of the manufacturing process.

U.S. Pat. No. 4,540,602 (Motoyama et al.) discloses a solid drug pulverized in an aqueous solution of a water-soluble high molecular substance using a wet grinding machine. However, Motoyama et al. teach that as a result of such wet grinding, the drug is formed into finely divided particles ranging from 0.5 μm (500 nm) or less to 5 μm (5,000 nm) in diameter.

EPO 275,796 describes the production of colloidally dispersible systems comprising a substance in the form of spherical particles smaller than 500 nm. However, the method involves a precipitation effected by mixing a solution of the substance and a miscible non-solvent for the substance and results in the formation of non-crystalline nanoparticle. Furthermore, precipitation techniques for preparing particles tend to provide particles contaminated with solvents. Such solvents are often toxic and can be very difficult, if not impossible, to adequately remove to pharmaceutically acceptable levels to be practical.

U.S. Pat. No. 4,107,288 describes particles in the size range from 10 to 1,000 nm containing a biologically or pharmacodynamically active material. However, the particles comprise a crosslinked matrix of macromolecules having the active material supported on or incorporated into the matrix.

It would be desirable to provide stable dispersible drug particles in the submicron size range which can be readily prepared and which do not appreciably flocculate or agglomerate due to interparticle attractive forces and do not require the presence of a crosslinked matrix. Moreover, it would be highly desirable to provide pharmaceutical compositions having enhanced bioavailability.

SUMMARY OF THE INVENTION

We have discovered stable, dispersible drug nanoparticles and a method for preparing such particles by wet milling in the presence of grinding media in conjunction with a surface modifier. The particles can be formulated into pharmaceutical compositions exhibiting remarkably high bioavailability.

More specifically, in accordance with this invention, there are provided particles consisting essentially of a crystalline drug substance having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm.

This invention also provides a stable dispersion consisting essentially of a liquid dispersion medium and the above-described particles dispersed therein.

In another embodiment of the invention, there is provided a method of preparing the above-described particles comprising the steps of dispersing a drug substance in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the drug substance to an effective average particle size of less than about 400 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

In a particularly valuable and important embodiment of the invention, there is provided a pharmaceutical composition comprising the above-described particles and a pharmaceutically acceptable carrier therefor. Such pharmaceutical composition is useful in a method of treating mammals.

It is an advantageous feature that a wide variety of surface modified drug nanoparticles free of unacceptable contamination can be prepared in accordance with this invention.

It is another advantageous feature of this invention that there is provided a simple and convenient method

for preparing drug nanoparticles by wet milling in conjunction with a surface modifier.

Another particularly advantageous feature of this invention is that pharmaceutical compositions are provided exhibiting unexpectedly high bioavailability.

Still another advantageous feature of this invention is that pharmaceutical compositions containing poorly water soluble drug substances are provided which are suitable for intravenous administration techniques.

Other advantageous features will become readily apparent upon reference to the following Description of Preferred Embodiments.

DESCRIPTION OF PREFERRED EMBODIMENTS

This invention is based partly on the discovery that drug particles having an extremely small effective average particle size can be prepared by wet milling in the presence of grinding media in conjunction with a surface modifier, and that such particles are stable and do not appreciably flocculate or agglomerate due to interparticle attractive forces and can be formulated into pharmaceutical compositions exhibiting unexpectedly high bioavailability. While the invention is described herein primarily in connection with its preferred utility, i.e., with respect to nanoparticulate drug substances for use in pharmaceutical compositions, it is also believed to be useful in other applications such as the formulation of particulate cosmetic compositions and the preparation of particulate dispersions for use in image and magnetic recording elements.

The particles of this invention comprise a drug substance. The drug substance exists as a discrete, crystalline phase. The crystalline phase differs from a noncrystalline or amorphous phase which results from precipitation techniques, such as described in EPO 275,796 cited above.

The invention can be practiced with a wide variety of drug substances. The drug substance preferably is present in an essentially pure form. The drug substance must be poorly soluble and dispersible in at least one liquid medium. By "poorly soluble" it is meant that the drug substance has a solubility in the liquid dispersion medium of less than about 10 mg/ml, and preferably of less than about 1 mg/ml. A preferred liquid dispersion medium is water. However, the invention can be practiced with other liquid media in which a drug substance is poorly soluble and dispersible including, for example, aqueous salt solutions, safflower oil and solvents such as ethanol, t-butanol, hexane and glycol. The pH of the aqueous dispersion media can be adjusted by techniques known in the art.

Suitable drug substances can be selected from a variety of known classes of drugs including, for example, analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillins), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives (hypnotics and neuroleptics), astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants (expectorants and mucolytics), diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics (antiparkinsonian agents), haemostatics, immuriological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators and xanthines. Preferred drug substances include those intended for oral administration and intravenous administration. A description of these classes of drugs and a listing of species within each class can be found in Martindale, The Extra Pharmacopoeia, Twenty-ninth Edition, The Pharmaceutical Press, London, 1989, the disclosure of which is hereby incorporated by reference in its entirety. The drug substances are commercially available and/or can be prepared by techniques known in the art.

Representative illustrative species of drug substances useful in the practice of this invention include:

17-α-pregno-2,4-dien-20-yno-[2,3-d]-isoxazol-17-ol (Danazol);

5α,17α,-1'-(methylsulfonyl)-1'H-pregn-20-yno[3,2-c]-pyrazol-17-ol (Steroid A);

piposulfam;

piposulfan;

camptothecin; and

ethyl-3,5-diacetoamido-2,4,6-triiodobenzoate

In particularly preferred embodiments of the invention, the drug substance is a steriod such as danazol or Steroid A or an antiviral agent.

The particles of this invention contain a discrete phase of a drug substance as described above having a surface modifier adsorbed on the surface thereof. Useful surface modifiers are believed to include those which physically adhere to the surface of the drug substance but do not chemically bond to the drug.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available Tweens, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethycellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986, the disclosure of which is hereby incorporated by reference in its entirety. The surface modifiers are commercially available and/or can be prepared by techniques known in the art.

Particularly preferred surface modifiers include polyvinyl pyrrolidone, Pluronic F68 and F108, which are block copolymers of ethylene oxide and propylene oxide, Tetronic 908, which is a tetrafunctional block copolymer derived from sequential addition of ethylene

oxide and propylene oxide to ethylenediamine, dextran, lecithin, Aerosol OT, which is a dioctyl ester of sodium sulfosuccinic acid, available from American Cyanamid, Duponol P, which is a sodium lauryl sulfate, available from DuPont, Triton X-200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas, Tween 80, which is a polyoxyethylene sorbitan fatty acid ester, available from ICI Specialty Chemicals, and Carbowax 3350 and 934, which are polyethylene glycols available from Union Carbide. Surface modifiers which have found to be particularly useful include polyvinylpyrrolidone, Pluronic F-68, and lecithin.

The surface modifier is adsorbed on the surface of the drug substance in an amount sufficient to maintain an effective average particle size of less than about 400 nm. The surface modifier does not chemically react with the drug substance or itself. Furthermore, the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages.

As used herein, particle size refers to a number average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation. By "an effective average particle size of less than about 400 nm" it is meant that at least 90% of the particles have a weight average particle size of less than about 400 nm when measured by the above-noted techniques. In preferred embodiments of the invention, the effective average particle size is less than about 250 nm. In some embodiments of the invention, an effective average particle size of less than about 100 nm has been achieved. With reference to the effective average particle size, it is preferred that at least 95% and, more preferably, at least 99% of the particles have a particle size less than the effective average, e.g., 400 nm. In particularly preferred embodiments, essentially all of the particles have a size less than 400 nm. In some embodiments, essentially all of the particles have a size less than 250 nm.

The particles of this invention can be prepared in a method comprising the steps of dispersing a drug substance in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the drug substance to an effective average particle size of less than about 400 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

A general procedure for preparing the particles of this invention is set forth below. The drug substance selected is obtained commercially and/or prepared by techniques known in the art in a conventional coarse form. It is preferred, but not essential, that the particle size of the coarse drug substance selected be less than about 100 μm as determined by sieve analysis. If the coarse particle size of the drug substance is greater than about 100 μm, then it is preferred that the particles of the drug substance be reduced in size to less than 100 μm using a conventional milling method such as airjet or fragmentation milling.

The coarse drug substance selected can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of the drug substance in the liquid medium can vary from about 0.1-60%, and preferably is from 5-30% (w/w). It is preferred, but not essential, that the surface modifier be present in the premix. The concentration of the surface modifier can vary from about 0.1 to about 90%, and preferably is 1-75%, more preferably 20-60%, by weight based on the total combined weight of the drug substance and surface modifier. The apparent viscosity of the premix suspension is preferably less than about 1000 centipoise

The premix can be used directly by subjecting it to mechanical means to reduce the average particle size in the dispersion to less than 400 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the drug substance and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation, e.g., a roller mill or a Cowles type mixer, until a homogeneous dispersion is observed in which there are no large agglomerates visible to the naked eye. It is preferred that the premix be subjected to such a premilling dispersion step when a recirculating media mill is used for attrition.

The mechanical means applied to reduce the particle size of the drug substance conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, and media mills such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the intended result, i.e., the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is from about 100 to about 1000 centipoise. For ball milling, the apparent viscosity of the premix preferably is from about 1 up to about 100 centipoise. Such ranges tend to afford an optimal balance between efficient particle fragmentation and media erosion.

The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of material for the grinding media is not believed to be critical. We have found that zirconium oxide, such as 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are believed to be acceptable for the preparation of pharmaceutical compositions. However, other media, such as stainless steel, titania, alumina, and 95% ZrO stabilized with yttrium, are expected to be useful. Preferred media have a density greater than about 3 g/cm^3.

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For ball mills, processing times of up to five days or longer may be required. On the other hand, processing times of less than 1 day (residence times of one minute up to several hours) have provided the desired results using a high shear media mill.

The particles must be reduced in size at a temperature which does not significantly degrade the drug substance. Processing temperatures of less than about 30°-40° C. are ordinarily preferred. If desired, the processing equipment can be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process. For example, ambient processing pressures are typical of ball mills, attritor mills and vibratory mills. Processing pressures up to about 20 psi (1.4 kg/cm^2) are typical of media milling.

The surface modifier, if it was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed, e.g., by shaking vigorously. Optionally, the dispersion can be subjected to a sonication step, e.g., using an ultrasonic power supply. For example, the dispersion can be subjected to ultrasonic energy having a frequency of 20–80 kHz for a time of about 1 to 120 seconds.

The relative amount of drug substance and surface modifier can vary widely and the optimal amount of the surface modifier can depend, for example, upon the particular drug substance and surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, etc. The surface modifier preferably is present in an amount of about 0.1–10 mg per square meter surface area of the drug substance. The surface modifier can be present in an amount of 0.1–90%, preferably 20–60% by weight based on the total weight of the dry particle.

As indicated by the following examples, not every combination of surface modifier and drug substance provides the desired results. Consequently, the applicants have developed a simple screening process whereby compatible surface modifiers and drug substances can be selected which provide stable dispersions of the desired particles. First, coarse particles of a selected drug substance of interest are dispersed in a liquid in which the drug is essentially insoluble, e.g., water at 5% (w/w) and milled for 60 minutes in a DYNO-MILL under the standard milling conditions which are set forth in Example 1 which follows. The milled material is then divided into aliquots and surface modifiers are added at concentrations of 2, 10 and 50% by weight based on the total combined weight of the drug substance and surface modifier. The dispersions are then sonicated (1 minute, 20 kHz) to disperse agglomerates and subjected to particle size analysis by examination under an optical microscope (1000× magnification). If a stable dispersion is observed, then the process for preparing the particular drug substance surface modifier combination can be optimized in accordance with the teachings above. By stable it is meant that the dispersion exhibits no flocculation or particle agglomeration visible to the naked eye at least 15 minutes, and preferably, at least two days or longer after preparation.

The resulting dispersion of this invention is stable and consists of the liquid dispersion medium and the above-described particles. The dispersion of surface modified drug nanoparticles can be spray coated onto sugar spheres or onto a pharmaceutical excipient in a fluid-bed spray coater by techniques well known in the art.

Pharmaceutical compositions according to this invention include the particles described above and a pharmaceutically acceptable carrier therefor. Suitable pharmaceutically acceptable carriers are well known to those skilled in the art. These include non-toxic physiologically acceptable carriers, adjuvants or vehicles for parenteral injection, for oral administration in solid or liquid form, for rectal administration, and the like. A method of treating a mammal in accordance with this invention comprises the step of administering to the mammal in need of treatment an effective amount of the above-described pharmaceutical composition. The selected dosage level of the drug substance for treatment is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore, depends upon the particular drug substance, the desired therapeutic effect, on the route of administration, on the desired duration of treatment and other factors. As noted, it is a particularly advantageous feature that the pharmaceutical compositions of this invention exhibit unexpectedly high bioavailability as illustrated in the examples which follow. Furthermore, it is contemplated that the drug particles of this invention provide more rapid onset of drug action and decreased gastrointestinal irritancy.

It is contemplated that the pharmaceutical compositions of this invention will be particularly useful in oral and parenteral, including intravenous, administration applications. It is expected that poorly water soluble drug substances, which prior to this invention, could not have been administered intravenously, may be administered safely in accordance with this invention. Additionally, drug substances which could not have been administered orally due to poor bioavailability may be effectively administered in accordance with this invention.

While applicants do not wish to be bound by theoretical mechanisms, it is believed that the surface modifier hinders the flocculation and/or agglomeration of the particles by functioning as a mechanical or steric barrier between the particles, minimizing the close, interparticle approach necessary for agglomeration and flocculation. Alternatively, if the surface modifier has ionic groups, stabilization by electrostatic repulsion may result. It was surprising that stable drug particles of such a small effective average particle size and free of unacceptable contamination could be prepared by the method of this invention.

The following examples further illustrate the invention.

EXAMPLE 1

PVP Modified Danazol Particles Prepared in a Ball Mill

A nanoparticulate dispersion of Danazol was prepared using a DYNO-MILL (Model KDL, manufactured by Willy A. Bachoffen AG Maschinenfabrik). The following ingredients were added to a glass vessel and agitated on a roller for 24 hours to dissolve the polyvinylpyrrolidone surface modifier.

Polyvinylpyrrolidone K-15 (made by GAF)—98 g
High purity water—664 g

Subsequently, 327 grams of dry powdered Danazol was added to the above solution and rolled for one week. This step aided in evenly dispersing the Danazol in the surface modifier solution, thereby reducing the treatment time required in the media mill. The Danazol was purchased in a micronized form (average particle size of about 10 microns) from Sterling Drug Inc. The particles had been prepared by a conventional airjet milling technique. This premix was added to a holding vessel and agitated with a conventional propeller mixer at low speed to maintain a homogeneous mixture for the media milling event. The media mill was prepared accordingly for the media milling process. The mill grinding chamber was partially filled with silica glass spheres and the premix was continuously recirculated through the media mill operating at the following conditions:

Grinding vessel: water jacketed stainless steel chamber
Premix flow rate: 250 ml per minute
Available volume of grinding vessel: 555 ml
Media volume: 472 ml of glass beads

Media type: size range of 0.5-0.75 mm silica glass beads, unleaded (distributed by Glen Mills, Inc.)

Recirculation time: 240 min

Residence time: 60 min

Impeller speed: 3000 RPM, tangential speed 1952 ft/min (595 m/min)

Grinding vessel coolant: water

Coolant temperature: 50° F. (10° C.)

After recirculating the slurry for 240 minutes, a sample of the dispersion was removed and evaluated for particle size distribution using a sedimentation field flow fractionator (made by DuPont). The particles were determined to have a number average diameter of 77.5 nm and a weight average diameter of 139.6 nm. The particle size of the dispersion ranged in size from 3-320 nm.

EXAMPLE 2

PVP Modified Danazol Particles Prepared in a Ball Mill at Low Solids.

A nanoparticulate dispersion of Danazol was prepared using a ball mill process. A 600 ml cylindrical glass vessel (inside diameter=3.0 inches (7.6 cm)) was filled approximately halfway with the following grinding media:

Grinding media: zirconium oxide grinding spheres (made by Zircoa, Inc.)

Media size: 0.85-1.18 mm diameter

Media volume: 300 ml

The following dry ingredients were added directly to this glass vessel:

Danazol (micronized): 10.8 g

Polyvinylpyrrolidone K-15: 3.24 g

High purity water: 201.96 g

Danazol was purchased in the micronized form (average particle size 10 microns) from Sterling Drug Inc. and the polyvinylpyrrolidone was K-15 grade produced by GAF. The cylindrical vessel was rotated horizontally about its axis at 57% of the "critical speed". The critical speed is defined as the rotational speed of the grinding vessel when centrifuging of the grinding media occurs. At this speed the centrifugal force acting on the grinding spheres presses and holds them firmly against the inner wall of the vessel. Conditions that lead to unwanted centrifuging can be computed from simple physical principles.

After 5 days of ball milling, the slurry was separated from the grinding media through a screen and evaluated for particle size with the sedimentation field flow fractionator. The number average particle diameter measured was 84.9 nm and the weight average particle diameter was 169.1 nm. The particles varied in size from 26 to 340 nm. The amount and type of surface modifier was sufficient to provide colloidal stability to agglomeration and to maintain a homogeneous blend of ingredients assuring precise material delivery during subsequent processing steps.

BIOAVAILABILITY TESTING

Bioavailability of Danazol from the nanoparticulate dispersion described above was compared to that from a suspension of unmilled Danazol in fasted male beagle dogs. The unmilled material was prepared as a suspension in the same manner as the dispersion, with the exception of the ball milling process. Both formulations were administered to each of five dogs by oral gavage and plasma obtained via a cannula in the cephalic vein. Plasma Danazol levels were monitored over 24 hours.

The relative bioavailability of Danazol from the nanoparticulate dispersion was 15.9 fold higher than from the Danazol suspension containing Danazol particles having an average particle size of about 10 microns prepared by conventional airjet milling. Comparison of oral plasma levels with dose corrected plasma levels following intravenous administration of Danazol gave a mean absolute bioavailability (±SEM) of 82.3±10.1% for the nanoparticulate dispersion and 5.1±1.9% for the unmilled material.

EXAMPLE 3

PVP Modified Danazol Particles Prepared in a Ball Mill at High Solids

A nanoparticle dispersion of Danazol was prepared using 1 mm diameter glass grinding media (0.85-1.18 mm from Potters Industries). A cylindrical glass vessel having a diameter of 2.75 inches (7.0 cm) with a volume of 400 ml was charged with 212 ml of unleaded glass grinding media. The following ingredients were added to this vessel:

30.4 g of micronized Danazol

9.12 g of Polyvinylpyrrolidone K-15

112.48 g of high purity water

This vessel was rotated horizontally on its axis at a controlled rotational speed of 80.4 revolutions per minute (50% of critical speed) for 5 days. The slurry was immediately separated from the grinding media and evaluated for particle size and grinding media attrition using inductively coupled plasma emissions (ICP). The particle size measured with a sedimentation field flow fractionator yielded a number average diameter of 112.7 nm and a weight average diameter of 179.3 nm. The extent of media attrition was measured to establish the purity of the final dispersion using an inductively coupled plasma-atomic emission spectroscopy method. The level of silicon in the final dispersion was less than 10 parts of elemental silicon per million parts of the slurry.

EXAMPLE 4

PVP Modified Danazol Particles

A nanoparticle dispersion of Danazol was prepared for clinical evaluation using a ball milling dispersion method. This dispersion was prepared by milling with glass grinding media. The grinding media used was:

Media type: 0.85-1.18 mm unleaded glass spheres

Media quantity: 6100 ml

The media was added to a 3 gallon porcelain jar. The following ingredients were then added to the jar:

1000 g Danazol (micronized)

300 g Polyvinylpyrrolidone K-15

3700 g high purity water

The vessel was rolled 5 days at a rotational speed of 39.5 revolutions per minute (50% critical speed). The liquid slurry was separated from the grinding media with a screen and used to prepare solid oral doses for clinical studies. The dispersion was assessed for particle size using the sedimentation field flow fractionator and was measured to have a number average diameter of 134.9 nm and a weight average diameter of 222.2 nm. The level of contamination from the grinding media was measured (by ICP) to be 36 parts of silicon per million parts of dispersion. Less than 5 ppm of aluminum was detected. X-ray powder diffraction data of the starting powder was compared with the dispersed Danazol and showed the crystal structure morphology

of the solid dispersed particles was unchanged by the dispersion process.

EXAMPLE 5

PVP Modified Danazol Particles

A nanoparticulate dispersion of Danazol was prepared using a laboratory media mill and glass grinding media. The media mill was equipped with a 50 ml grinding chamber and the mill was a "Mini" Motormill manufactured by Eiger Machinery Inc.

The media mill was operated at the following process conditions:

Bead charge: 42.5 ml glass spheres

Rotor speed: 5000 RPM (2617 feet per minute (798 m/min) tangential speed)

Grinding media: 0.75-1.0 mm unleaded glass beads (distributed by Glens Mills)

The dispersion formula was prepared by dissolving 27 g of polyvinylpyrrolidone in 183 g of water and agitated in a steel vessel with a 50 mm "Cowles" type blade until the solution was clear and free of undissolved PVP polymer. The rotational speed of the mixer was maintained at 5000 RPM. 90 g of micronized Danazol was slowly added to this blend with the same mixing for 30 min. 200 cc of the premix was added to the holding tank of the mill and recirculated for 5 hours and 51 minutes. The final residence time in the grinding zone was 40 minutes.

The final average particle size was measured and determined to have a number average diameter of 79.9 nm and a weight average diameter of 161.2 nm. The particles varied in size from 30-415 nm. The level of attrition from erosion of the grinding media and grinding vessel were measured (by ICP) to be 170 ppm of iron and 71 ppm silicon. The crystal structure was determined by X-ray diffraction to be unchanged by the dispersion process.

EXAMPLE 6

Lecithin Modified Steroid A Particles

A nanoparticulate dispersion of Steroid A was prepared by ball milling with zirconium oxide grinding beads. The dispersion was prepared in the absence of a surface modifier and a post addition of Lecithin and a sonication step were required to stablize the dispersed phase of Steroid A and prevent agglomeration and rapid sedimentation. A fine particle dispersion of Steroid A was prepared by ball milling the following ingredients:

5 g Steroid A

95 g high purity water

Steroid A was in the form of unmilled coarse grains having a particle size of about 100 μm and ranging in size up to about 400 μm.

The following process conditions were used:

Media: 135 ml

Vessel volume: 240 ml

Media type: 0.85-1.18 mm Zirbeads (manufactured by Zircoa Inc.)

Milling time: 4 days

Milling speed: 86 RPM (50% critical speed)

After four days of ball milling the slurry was separated from the grinding media through a screen. One gram of this unstabilized slurry was added to 10 g of an aqueous solution of Lecithin (1% Centrolex "P" by weight in high purity water, Lecithin manufactured by Central Soya Company, Inc.) and mixed by vigorous shaking, followed by a sonication step for 20 seconds using an ultrasonic horn (Model 350 Branson Ultrasonic Power Supply, Horn Diameter=0.5 inch (1.27 cm), Power setting=2). The slurry was sized under a microscope. An Olympus BH-2 optical microscope equipped with phase contrast illumination was used to observe the size and condition of the dispersion.

A drop of the above dilute slurry was placed between a microscope slide and glass cover slip and observed microscopically at high magnification (1,000 times) and compared to the slurry similarly diluted with water only (no surface modifier). The unmodified dispersion exhibited extensive particle agglomeration. The particle size of the unmodified dispersion was more than 10 microns and the unmodified dispersion exhibited no Brownian Motion. Brownian motion is the oscillatory or jiggling motion exhibited by particles in a liquid that fall in the size range of less than about 1 micron. The Lecithin modified particles exhibited rapid Brownian motion. The thus observed dispersion had the characteristics and appearance consistent with a number average particle size of less than 400 nm. Furthermore, it is expected that additional milling would lead to further particle size reduction.

EXAMPLE 7

Alkyl Aryl Polyether Sulfonate Modified Steroid A

Example 6 was repeated except that the Lecithin was replaced with Triton X-200 (manufactured by Rohm and Haas). Similar results were observed.

EXAMPLE 8

Gum Acacia Modified Steroid A

Example 6 was repeated except that the Lecithin was replaced with gum acacia (available from Eastman Kodak Co.) Similar results were observed.

EXAMPLE 9

Sodium Lauryl Sulfate Modified Steroid A

Example 6 was repeated except that the Lecithin was replaced with sodium lauryl sulfate (available as Duponol ME from DuPont, Inc.). Similar results were observed.

EXAMPLE 10

Steroid A Modified with a Dioctylester of Sodium Sulfosuccinic Acid

Example 6 was repeated except that the Lecithin was replaced with Aerosol OT (available from American Cyanamid Chemical Products, Inc.). Similar results were observed.

EXAMPLE 11

Steroid A Modified with a Block Copolymer of Ethylene Oxide and Propylene Oxide

Example 6 was repeated except that the Lecithin was replaced with Pluronic F68 (available from BASF Corp.). Similar results were observed.

EXAMPLE 12

Steroid A Modified with a Block Copolymer of Ethylene Oxide and Propylene Oxide

A nanoparticulate dispersion of Steroid A was prepared by ball milling with zirconium oxide grinding

media for 5 days. 70 cc of grinding media were added to a 115 cc vessel followed by:

2.5 g Steroid A

0.75 g of Pluronic F68

46.75 g high purity water

The resulting mixture was ball milled for 5 days at 50% of the critical rotational speed. The final dispersion was separated from the grinding media and microscopically evaluated for particle size as in Example 6. The dispersion exhibited rapid Brownian Motion and no particles were larger than 1 micron. Most particles were less than 400 nm.

EXAMPLE 13

Lecithin Modified Steroid A Particles

Example 12 was repeated except that the Pluronic F68 was replaced with Centrolex P. No particles larger than 1 micron were observed microscopically and most were less than 400 nm.

EXAMPLE 14

Steroid A Particles Modified with a Block Copolymer of Ethylene Oxide and Propylene Oxide

A nanoparticulate dispersion of Steroid A was prepared by a ball milling process. The following ingredients were added to a cylindrical 0.95 l vessel. The vessel was filled approximately halfway with the following grinding media:

Grinding media: 0.85–1.18 mm diameter zirconium oxide spheres (made by Zircoa)

The following dispersion ingredients were added directly to the glass vessel:

18 g Steroid A

4.5 g Pluronic F68 (purchased from BASF Corp.)

336.6 g high purity water

Steroid A was purchased from Sterling Drug Inc. in the form of unmilled tabular crystals having an average particle size of approximately 100 μm.

The vessel was rotated concentrically on its axis at 50% critical speed for 5 days. After this time 4.45 g of Pluronic F68 was added to the slurry and rolled for 5 more days at the same conditions. The slurry was then discharged and separated from the grinding media and evaluated for particle size using the sedimentation field flow fractionator. The number average particle size measured was 204.6 nm and the weight average particle size was 310.6 nm. The particle size distribution ranged from approximately 68–520 nm. The dispersion was examined with an optical microscope. It exhibited excellent particle integrity, free flocculation and agglomeration. The dispersion particles exhibited rapid Brownian motion.

BIOAVAILABILITY TESTING

Bioavailability of Steroid A from the nanoparticulate dispersion described above was compared to that from a suspension of unmilled Steroid A (having an average particle size of about 100 μm) in male beagle dogs. The unmilled material was prepared as a suspension in the same manner as the dispersion, with the exception of the ball milling process. Both formulations were administered to each of five dogs by oral gavage and plasma obtained via a cannula in the cephalic vein. Plasma Steroid A levels were monitored over 24 hours. The relative bioavailability of Steroid A from the nanoparticulate dispersion was 7.1 fold higher than from the unmilled Steroid A suspension. Comparison of oral plasma levels with dose corrected plasma levels following intravenous administration of Steroid A gave a mean absolute bioavailability (±SEM) of 14.8±3.5% for the nanoparticulate dipersion and 2.1±1.0% for the unmilled material.

COMPARATIVE EXAMPLE A

A dispersion of Steroid A was prepared using a ball milling process with zirconium oxide grinding beads. The dispersion was prepared in the absence of a surface modifier and a post-sonication step was used to minimize flocculation and reaggregation.

A fine particle dispersion was prepared by ball milling the following ingredients:

5 g Steroid A

95 g high purity water

The following process conditions were used:

Grinding media: 135 ml

Vessel volume: 240 ml

Grinding media: 0.85–1.18 mm Zirbeads XR

Milling time: 4 days

Milling speed: 86 RPM (50% critical speed)

After four days of ball milling, the slurry was separated from the grinding media through a screen. One gram of the unstablized slurry was blended with 10 grams of high purity water and mixed by vigorous shaking, followed by a sonication step for 20 seconds using an ultrasonic horn (Model 350 Branson Ultrasonic Power Supply, Horn diameter=0.5 inch, Power setting=2). The slurry was sized under a microscope. An optical microscope equipped with phase contrast illumination was used to observe the condition of the dispersion.

A drop of the dilute slurry was placed between a microscope slide and a glass cover slip and observed at high magnification (400×). The dispersion exhibited severe particle aggregation. The aggregate size was greater than 10 microns and exhibited no Brownian particle movement.

COMPARATIVE EXAMPLE B

Comparative Example A was repeated except that 1 gram of the slurry was added to 10 grams of a dilute solution (1% by weight) of PVP K-15. The resultant dispersion after 6 days was aggregated. The aggregate size was at least 5 microns. After 6 days of holding, the dispersion settled completely leaving a clear supernatant and a layer of Steroid A sediment.

COMPARATIVE EXAMPLE C

Comparative Example B was repeated except that the 1% PVP solution was replaced with a 1% solution of purified sodium methyl oleoyl taurate (available from GAF as Igepon T and subsequently purified at Eastman Kodak). After 6 days the dilute dispersion was partially flocculated and had many aggregates larger than 1 micron.

COMPARATIVE EXAMPLE D

Comparative Example B was repeated except that 1 gram of slurry was added to 10 grams of a 1% aqueous solution of polyethylene glycol (available from Union Carbide as PEG 3350). The dispersion after sonification was flocculated with particles larger than 35 microns.

COMPARATIVE EXAMPLE E

Comparative Example B was repeated except that the dispersion was diluted with an aqueous 1% solution of

gum tragacanth (available from Eastman Kodak). This freshly prepared dispersion exhibited flocculation with particles 10 microns and larger.

COMPARATIVE EXAMPLE F

A dispersion of Danazol was prepared by ball milling with zirconium oxide grinding spheres. A cylindrical glass vessel was filled about halfway with the following ingredients:

Grinding media: 135 ml 0.85–1.18 mm Zirbeads XR
5 g Danazol
1 g PVP K-15
94 g high purity water

This vessel was rotated horizontally on its axis at a controlled speed of 50% critical speed (85 RPM) for 4 days. The slurry was discharged and separated from the grinding media through a screen and examined for particle size with an optical microscope. The slurry was examined for particle size after holding it for 4 days at room temperature (23° C.). A drop of undiluted slurry was placed between a glass microscope slide and a glass cover slip and observed optically at high magnification (400X). The slurry was partially aggregated with particles up to 10 microns in diameter. Unlike Examples 1–5, the amount of PVP present was insufficient to hinder particle agglomeration.

The invention has been described in detail with particular reference to preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

What is claimed is:

1. Particles consisting essentially of 99.9–10% by weight of a crystalline drug substance having a solubility in water of less than 10 mg/ml, said drug substance having a non-crosslinked surface modifier adsorbed on the surface thereof in an amount of 0.1–90% by weight and sufficient to maintain an effective average particle size of less than about 400 nm.

2. The particles of claim 1 having an effective average particle size of less than 250 nm.

3. The particles of claim 1 having an effective average particle size of less than 100 nm.

4. The particles of claim 1 wherein said drug substance is selected from analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives, astringents, beta-adrenoceptor blocking agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immuriological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, sympathomimetics, thyroid agents, vasodilators and xanthines.

5. The particles of claim 1 wherein said drug substance is a steroid.

6. Particles consisting essentially of 99.9–10% by weight of a crystalline drug substance having a solubility in water of less than 10 mg/ml, said drug substance having a non-crosslinked surface modifier absorbed on the surface thereof in an amount of 0.1–90% by weight and sufficient to maintain an effective average particle size of less than about 400 nm, wherein said drug substance is selected from the group consisting of Danazol, 5α,17α,-1'-(methylsulfonyl)-1'H-pregn-20-yno-[3,2-c]-pyrazol-17-ol, piposulfam, piposulfan, camptothecin, and ethyl-3,5-diacetamido-2,4,6-triiodobenzoate.

7. The particles of claim 1 wherein said surface modifier is selected from the group consisting of gelatin, casein, lecithin, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene caster oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethycellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone.

8. The particles of claim 1 wherein said surface modifier is selected from the group consisting of polyvinylpyrrolidone, an ethylene oxide-propylene oxide block copolymer, lecithin, an alkyl aryl polyether sulfonate, gum acacia, sodium dodecylsulfate, and a dioctylester of sodium sulfosuccinic acid.

9. Particles consisitng essentially of 80–40% by weight of crystalline danazol having polyvinyl pyrrolidone adsorbed on the surface thereof in an amount of 20–60% by weight and sufficient to maintain an effective average particle size of less than about 100 nm.

10. Particles consisting essentially of 99.9–10% by weight of crystalline 5α, 17α,-1'-(methylsulfonyl)-1'H-pregn-20-yno-pyrazol-17-ol having an ethylene oxide propylene-oxide block copolymer adsorbed on the surface thereof in an amount of 0.1–90% by weight and sufficient to maintain an effective average particle size of less than about 400 nm.

11. A stable dispersion consisting essentially of a liquid dispersion medium and the particles of claim 1.

12. The dispersion of claim 11 wherein said dispersion medium is water.

13. The dispersion of claim 11 wherein said dispersion medium is selected from the group consisting of safflower oil, ethanol, t-butanol, hexane and glycol.

14. A pharmaceutical composition comprising the particles of claim 1 and a pharmaceutically acceptable carrier therefor.

15. A method of treating a mammal comprising the step of administering to the mammal an effective amount of the pharmaceutical composition of claim 14.

16. A method of preparing the particles of claim 1 comprising the steps of dispersing a drug substance in a liquid dispersion medium and wet grinding said drug substance in the presence of rigid grinding media having an average particle size of less than 3 mm and a surface modifier to reduce the particle size of said drug substance to an effective average particle size of less than about 400 nm.

17. A method of preparing the particles of claim 1 comprising the steps of dispersing a drug substance in a liquid dispersion medium, wet grinding said drug substance in the presence of rigid grinding media having an average particle size of less than 3 mm, thereafter contacting said drug substance with a surface modifier by mixing said surface modifier with said dispersion me-

dium to form particles having an effective average particle size of less than about 400 nm.

18. The method of claim 17 further including the step of subjecting the dispersion medium containing said drug substance and said surface modifier to ultrasonic energy.

19. The method of claim 16 wherein said grinding media have an average particle size of less than 1 mm.

20. The method of claim 16 wherein said grinding media have a density greater than 3 g/cm^3.

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United States Patent [19]

Kuczynski et al.

[11] **Patent Number: 5,024,843**

[45] **Date of Patent: Jun. 18, 1991**

[54] **ORAL HYPOGLYCEMIC GLIPIZIDE GRANULATION**

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[52] **U.S. Cl.** **424/499;** 424/80; 424/473; 424/501; 514/866

[58] **Field of Search** 424/475, 494, 499

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[57] **ABSTRACT**

A dosage form is disclosed comprising the antidiabetic drug glipizide for administering to a patient in need of glipizide therapy.

2 Claims, 2 Drawing Sheets

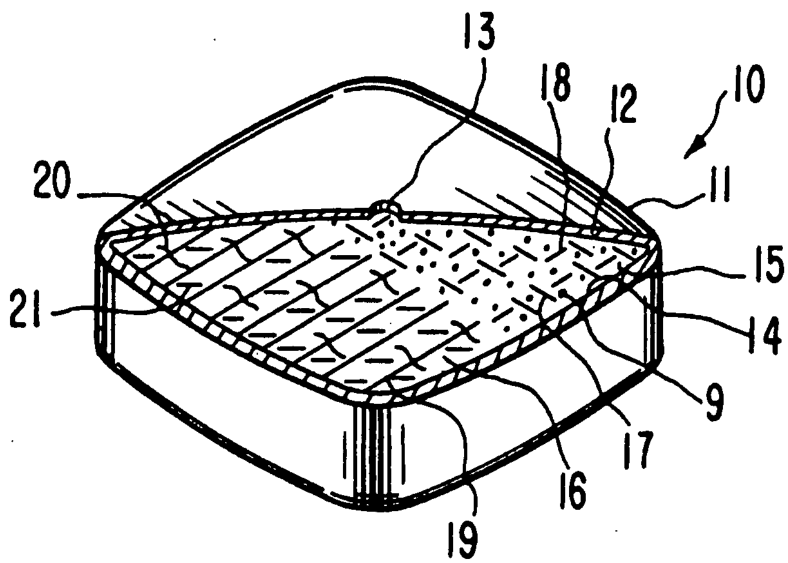


FIG. 1

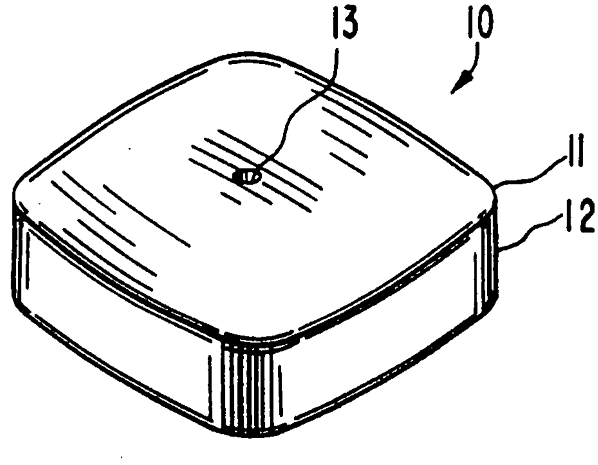


FIG. 2

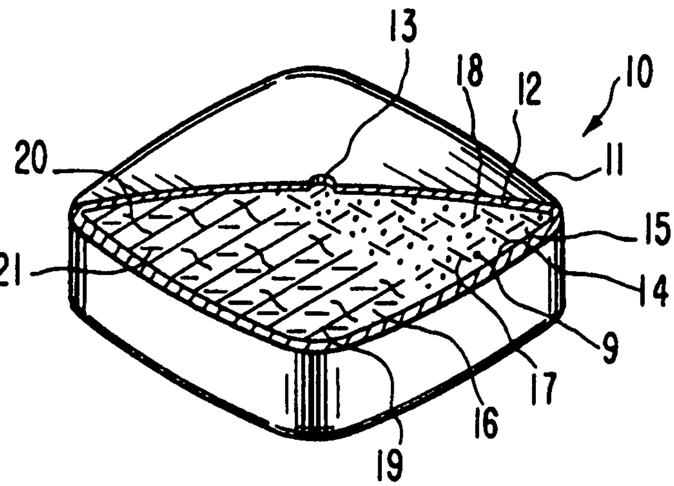


FIG. 3

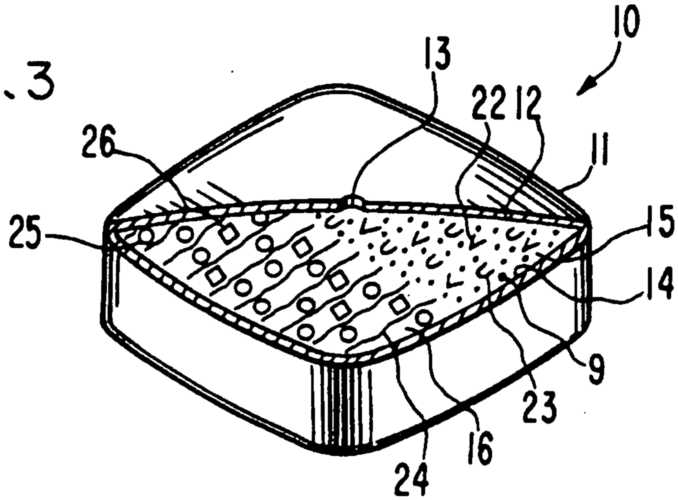


FIG. 4

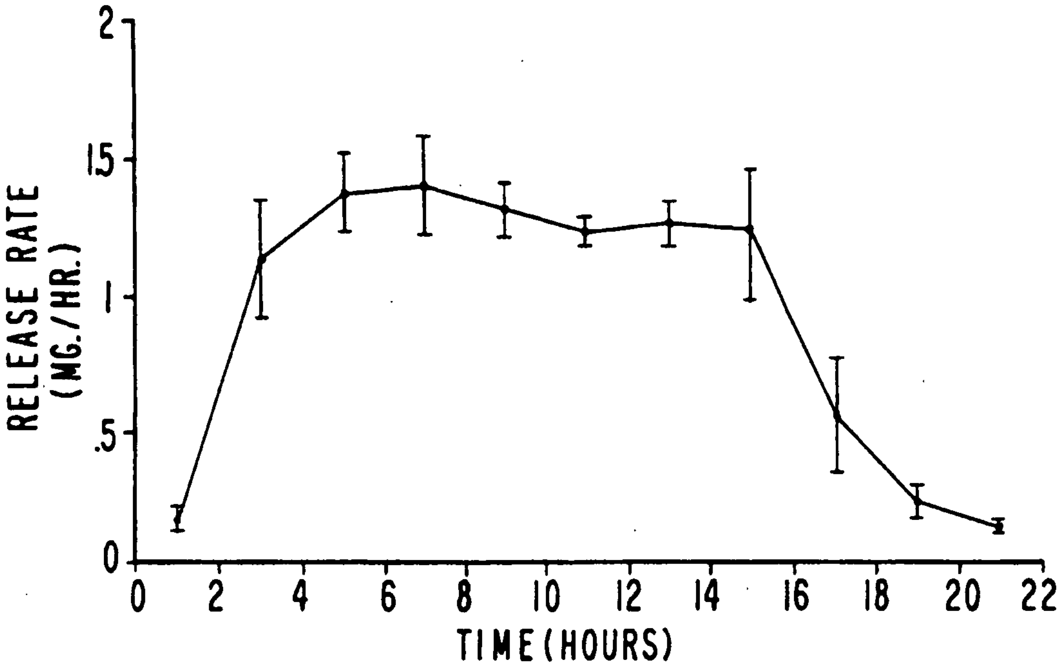
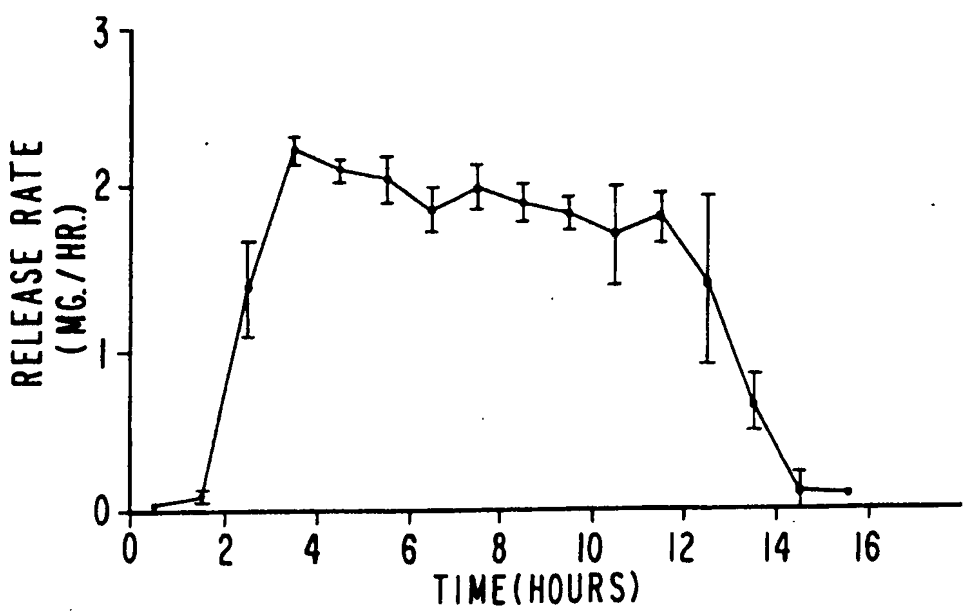

RELEASE RATE (MG./HR.)
2
1.5
1
.5
0
0 2 4 6 8 10 12 14 16 18 20 22
TIME (HOURS)

FIG. 5


RELEASE RATE (MG./HR.)
3
2
1
0
0 2 4 6 8 10 12 14 16
TIME (HOURS)

ORAL HYPOGLYCEMIC GLIPIZIDE GRANULATION

DISCLOSURE OF TECHNICAL FIELD

This invention pertains to a dosage form comprising the hypoglycemic drug glipizide. The invention concerns also a method for administering glipizide to a recipient in need of glipizide therapy.

DISCLOSURE OF BACKGROUND OF THE INVENTION

A clinical need exists for a dosage form for delivering an oral blood-glucose lowering drug to a patient needing this therapy. Glipizide is an oral blood-glucose lowering drug and it is indicated for the control of hyperglycemia and its associated symptomatology in patients with non-insulin dependent diabetes mellitus. Glipizide is useful therapeutically as an oral hypoglycemic drug because it stimulates insulin secretion from the beta cells of pancreatic-islet tissue, it increases the concentration of insulin in the pancreatic vein, and because it exhibits extrapancreatic action such as the ability to increase the number of insulin receptors.

Glipizide is known chemically as N-[2-[4-[[[(cyclohexylamino) carbonyl]amino]sulfonyl]phenyl]ethyl]-5-methylpyrazinecarboxamide. Glipizide is a white, odorless powder with a pKa of 5.9, and it is insoluble in both water and alcohol. These physical and chemical properties of glipizide do not lend the drug to formulation into a dosage form that can administer glipizide at a controlled and known rate per unit time. The properties of glipizide are disclosed in *Martindale The Extra Pharmacoooeia.* 29th Ed., p 390, (1989); and, *AHFS Drug Information,* pp 1741–45, (1989).

In the light of the above presentation, it will be appreciated by those versed in the pharmaceutical dispensing art to which this invention pertains, that a pressing need exists for a rate-controlled dosage form that can deliver the valuable drug glipizide to a patient in clinical need of blood-glucose lowering therapy. The pressing need exists also for an oral dosage form that can deliver glipizide at a controlled rate in a substantially constant dose per unit time for its beneficial therapeutic effects, and remain substantially independent of the changing environment of the gastrointestinal tract. It will be appreciated further by those skilled in the dispensing art, that if such a novel and unique dosage form is made available that can administer glipizide in a rate-controlled dose over time, and simultaneously provide blood-glucose lowering therapy, the dosage form would represent an advancement and a valuable contribution to the medical art.

DISCLOSURE OF OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a dosage form for delivering glipizide in a rate controlled amount, and which dosage form substantially overcomes the deficiencies and omissions associated with the prior art.

Another object of the present invention is to provide a dosage form for orally administering glipizide in a rate-controlled dose for blood-glucose lowering therapy.

Another object of the invention is to provide a pharmaceutical dosage form that makes available controlled and sustained glipizide therapeutic activity to a patient in need of glipizide therapy.

Another object of the invention is to provide a novel dosage form manufactured as an osmotic device that can administer glipizide to a biological receptor site to produce the desired glipizide pharmacological effects.

Another object of the present invention is to provide a dosage form manufactured as an osmotic dosage form that maintains glipizide in the dosage form until released from the dosage form, thereby substantially reducing and/or substantially eliminating the unwanted influences of the gastrointestinal environment and still provide controlled administration of glipizide over time.

Another object of the present invention is to provide a dosage form that can deliver the aqueous insoluble drug glipizide at a controlled and beneficial known rate over time.

Another object of the present invention is to provide a dosage form adapted for the oral administration of glipizide and which dosage form comprise a first composition and a contacting second composition that operate in combination for the controlled administration of glipizide.

Another object of the present invention is to provide a complete pharmaceutical glipizide regimen comprising a composition comprising glipizide that can be dispensed from a drug delivery dosage form, the use of which requires intervention only for initiation and possibly for termination of the regimen.

Another object of the invention is to provide a method for treating hyperglycemia by orally administering glipizide in a ratecontrolled dose per unit time to a warm-blooded animal in need of hyperglycemia therapy.

Other objects, features and advantages of this invention will be more apparent to those versed in the dispensing arts from the following detailed specification, taken in conjunction with the drawings and the accompanying claims.

BRIEF DISCLOSURE OF THE DRAWINGS

In the drawings, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Drawing FIG. 1 is a view of a dosage form designed and shaped for orally administering glipizide to the gastrointestinal tract of a warm-blooded animal, including humans;

Drawing FIG. 2 is an opened view of the dosage form of drawing FIG. 1 illustrating the structure of the dosage form comprising glipizide;

Drawing FIG. 3 is an opened view of the dosage form of drawing FIG. 1 depicting a different internal structure embodiment provided by the invention;

Drawing FIG. 4 is a graph that depicts the release rate pattern from one embodiment of the dosage form provided by the invention; and,

Drawing FIG. 5 is a graph that depicts the release rate pattern for a different embodiment of the dosage form provided by the invention.

In the drawing figures and in the specification like parts in related drawing figures are identified by like numbers. The terms appearing earlier in the specification and in the description of the drawings, as well as embodiments thereof, are further described elsewhere in the disclosure.

DETAILED DISCLOSURE OF THE DRAWING FIGURES

Turning now to the drawing figures in detail, which drawing figures are examples of the dosage forms provided by this invention, and which examples are not to be construed as limiting, one example of the dosage form is illustrated in drawing FIG. 1 and designated by the numeral **10**. In drawing FIG. 1, dosage form **10** comprises a body **11**, which body member **11** comprises a wall **12** that surrounds and encloses an internal compartment, not seen in drawing FIG. 1. Dosage form **10** comprises at least one exit means **13** for connecting the interior of dosage form **10** with the exterior environment of use.

In drawing FIG. 2, dosage form **10** is seen in opened view. In drawing FIG. 2, dosage form **10** comprises a body member **11** comprising wall **12**, which wall surrounds and defines an internal compartment **14**. Wall **12** comprises at least one exit means **13** that connects internal compartment **14** with the exterior of dosage form **10**. Dosage form **10** can comprise more than one exit means **13**. Wall **12** of dosage form **10** comprises in total, or in at least a part, a composition that is permeable to the passage of an exterior fluid present in the environment, and wall **12** is substantially impermeable to the passage of glipizide and other ingredients present in compartment **14**. The composition comprising wall **12** is semipermeable, it is substantially inert, and wall **12** maintains its physical and chemical integrity during the dispensing life of glipizide from dosage form **10**. The phrase, keeps its physical and chemical integrity, means wall **12** does not lose its structure, and it does not change chemically during the glipizide dispensing life of dosage form **10**.

Wall **12**, in a presently preferred embodiment, comprises 80 weight percent (wt%) to 100 weight percent of a composition comprising a cellulose polymer. The cellulose polymer comprises a member selected from the group consisting of a cellulose ester, cellulose ether, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, and cellulose triacetate. Wall **12**, in another preferred manufacture, comprises from 0 weight percent to 25 weight percent of a member selected from the group consisting of hydroxypropylcellulose and hydroxypropylmethylcellulose, and from 0 to 20 weight percent of polyethylene glycol, with the total amount of all wall-forming components comprising wall **12** equal to 100 weight percent.

Internal compartment **14** comprises an internal glipizide lamina **15**, which glipizide lamina can be defined optionally as a glipizide composition **15**. Internal compartment **14** also comprises an internal displacement lamina **16**, which displacement lamina can be defined optionally as a displacement composition **16**. The glipizide lamina **15** and the displacement lamina **16** initially are in laminar arrangement and they cooperate with each other and with dosage form **10** for the effective delivery of glipizide from dosage form **10**.

The glipizide composition **15**, in a presently preferred embodiment, as seen in FIG. 2, comprises about 2.0 mg to 50 mg of glipizide identified by dots **9**; from 100 mg to 320 mg of a polyethylene oxide comprising 80,000 to 350,000 molecular weight and identified by dashes **17**; from 5 mg to 50 mg of hydroxypropylmethylcellulose comprising a 9,200 to 22,000 molecular weight and identified by vertical lines **18**; and from 0 mg to 7.5 mg of a lubricant such as stearic acid, magnesium stearate, and the like.

The displacement lamina **16**, as seen in drawing FIG. 2, comprises 70 mg to 125 mg of a polyethylene oxide comprising a 4,000,000 to 8,000,000 molecular weight identified as lines **19**; from 20 mg to 50 mg of an osmagent selected from the group consisting of sodium chloride and potassium chloride identified by wavy line **20**; and from 5 mg to 15 mg of a hydroxypropylmethylcellulose having a 9,000 to 25,000 molecular weight identified by vertical slashes **21**. Displacement lamina **16** optionally comprises from 0.1 mg to 5 mg of ferric oxide and from 0.01 mg to 5 mg of a lubricant such as magnesium stearate or stearic acid.

Drawing FIG. 3 depicts in opened section another osmotic dosage form **10** provided by the invention. In drawing FIG. 3, dosage form **10** comprises a body **11**, a wall **12**, which wall **12** surrounds an internal compartment **14** with an exit passageway **13** in wall **12**. Internal compartment **14**, in this dosage form, comprises an internal glipizide lamina **15**, which glipizide lamina **15** comprises 2 mg to 25 mg of aqueous insoluble drug glipizide identified by dots **9**; from 100 mg to 150 mg of a hydroxypropylcellulose comprising a 40,000 to 80,000 molecular weight identified by angle **22**; and from 40 mg to 70 mg of a polyvinylpyrrolidone comprising a 30,000 to 70,000 molecular weight and identified by half circle **23**. Internal compartment **14** comprises a displacement lamina **16** comprising 30 mg to 150 mg of sodium carboxymethylcellulose having 200,000 to 1,000,000 molecular weight identified by wavy lines **24**; from 20 mg to 70 mg of an osmagent selected from the group consisting of sodium chloride and potassium chloride identified by circle **25**; and from 0.5 mg to 10 mg of a hydroxypropylmethylcellulose comprising a 9,200 to 22,000 molecular weight identified by squares **26**. Displacement lamina **16** optionally comprises from 0 mg to 5 mg of ferric oxide and optionally 0 mg to 7 mg of a lubricant.

The expression, "exit means 13,' as used herein, comprises means and methods suitable for the controlled metered release of glipizide **9** from compartment **14** of dosage form **10**. The exit means **13** comprises at least one passageway, orifice, or the like, through wall **12** for communication with glipizide **9** in compartment **14**. The expression, "at least one passageway,' includes aperture, orifice, bore, pore, or porous element through which glipizide can be released, or hollow fiber, capillary tube, porous overlay, porous insert, and the like. The expression also includes a material that erodes or is fluid-leached from wall **12** in a fluid environment of use to produce at least one pore-passageway of governed release rate pore-size in wall **12**. Representative materials suitable for forming at least one passageway, or a multiplicity of passageways, comprise an erodible polyglycolic acid, or a polylactic acid member in wall **12**, a gelatinous filament, polyvinyl alcohol, leachable materials such as a fluid removable pore forming polysaccharide, salt, oxide, polyol, or the like. A passageway or a plurality of passageways can be formed by leaching a material such as sorbitol, lactose, or the like, from wall **12**. The passageway can have any shape such as round, triangular, square, elliptical, and the like, for assisting in the metered release of glipizide **9** from dosage form **10**. Dosage form **10** can be constructed with one or more passageways in spaced apart relations, or more than one passageway on a single surface of dosage form **10**. Passageways and equipment for forming passageways are

disclosed in U.S. Pat. Nos. 3,845,770 issued 11/74 to Theeuwes et al; 3,916,899 issued 11/75 to Theeuwes et al; 4,016,880 issued 4/77 to Theeuwes et al; 4,063,064 issued 12/77 to Saunders et al; 4,088,864 issued 5/78 to Theeuwes et al; and, passageways formed by leaching are disclosed in U.S. Pat. Nos. 4,200,098 issued 4/80 to Ayer et al; 4,235,236 issued 11/80 to Theeuwes; and, 4,285,987 issued to Ayer et al.

Dosage form 10 of this invention is manufactured by standard techniques. For example, in one manufacture the drug glipizide is mixed with other composition-forming ingredients and the mix then pressed into a solid lamina possessing dimensions that correspond to the internal dimensions of the compartment space adjacent to the passageway. In another embodiment the beneficial drug glipizide and other composition forming ingredients and a solvent are mixed into a solid, or into a semisolid, by conventional methods such as ballmilling, calendering, stirring, or rollmilling, and then pressed into a preselected lamina forming shape. Next, a lamina composition comprising the osmopolymer and the osmagent are placed in contact with the lamina comprising the beneficial drug glipizide, and the two lamina comprising the laminate are surrounded with a semipermeable wall. The lamination of the glipizide composition and the osmopolymer displacement composition can be accomplished by using a two-layer tablet press technique. The wall can be applied by molding, spraying, or dipping the pressed shapes into wall-forming formulations. Another preferred technique that can be used for applying the wall is the air suspension coating procedure. This procedure consists in suspending and tumbling the two layered laminate in a current of air until the wall forming composition surrounds the laminate. The air suspension procedure is described in U.S. Pat. No. 2,799,241; in *J. Pharm. Assoc.. Sci. Ed.*, Vol. 48 pp 451-59 (1959); and *ibid.* Vol. 49, pp 82-84, (1960). Other standard manufacturing procedures are described in *Modern Plastics Encvclooedia.* Vol. 46, pp 62-70, (1969); and in *Pharmaceutical Sciences*, by Remington, 14th Ed., pp 1626-1978, (1970), published by Mack Publishing Co., Easton, PA.

Exemplary solvents suitable for manufacturing the wall, the laminate, and laminae, comprise inert inorganic and organic solvents that do not adversely affect the final wall and the final laminates. The solvents broadly comprise a member selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents, and mixtures thereof. Typical solvents comprise acetone, diacetone, alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methylpropyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, ethylene dichloride and methanol, and the like.

DETAILED DISCLOSURE OF EXAMPLES OF THE INVENTION

The following examples are merely illustrative of the present invention, and they should not be eonsidered as limiting the scope of this invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and the accompanying claims.

EXAMPLE 1

An oral dosage form, adapted, designed and shaped as an osmotic drug delivery system for admittance into the gastrointestinal tract of a patient in need of glipizide is manufactured as follows: first, 369 g of pharmaceutically acceptable hydroxypropylcellulose comprising a 60,000 average molecular weight is passed through a 20 mesh screen, followed by passing through a 40 mesh screen 162 g of pharmaceutically acceptable polyvinylpyrrolidone comprising a 40,000 average molecular weight. Next, the two screened ingredients are blended with 66 g of glipizide to form a homogeneous blend. The blend is suspended in a fluidized bed and sprayed with an atomized spray comprising an ethanol:water (70:30 vol:vol) solution until granules are formed of the three ingredients. The freshly prepared granules then are passed through a 20 mesh screen. Finally, the screened granulation is mixed with 3 g of magnesium stearate in a rollermill for 5 minutes.

Next, a separate hydrogel granulation is prepared as follows: first, 389 g of pharmaceutically acceptable sodium carboxymethylcellulose having 700,000 molecular weight, 174 g of sodium chloride, 30 g of pharmaceutically acceptable hydroxypropylmethylcellulose comprising a 11,200 molecular weight and 6 g of ferric oxide separately are screened through a 40 mesh screen. Then, all the screened ingredients are mixed to produce a homogeneous blend. Next, 300 ml of denatured anhydrous ethanol is added slowly to the blend with continuous mixing for about 5 minutes. The freshly prepared wet granulation is screened through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh screen. The screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for about 5 minutes.

Next, the glipizide granulation, and the hydrogel granulation are compressed into a bilaminate tablet arrangement. First, 200 mg of the glipizide composition is added to a 0.375 inch (9.5 mm) punch and tamped, then, 140 mg of the hydrogel granulation is added to the punch and the two laminae are pressed into a solid, contacting arrangement.

Next, the bilaminate is coated with a semipermeable wall. The semipermeable wall-forming composition comprises 93% cellulose acetate having a 39.8% acetyl content, and 7% polyethylene glycol having a 3350 molecular weight. The wall-forming composition is dissolved in a cosolvent comprising acetone: water (90:10 wt:wt) to onto and around the bilaminate in an Aeromatic® Air Suspension Coater.

Then, a 25 mil (0.635 mm) exit orifice is mechanically drilled on the glipizide side of the osmotic dosage form. The residual solvent is removed by drying the osmotic system for 48 hours at 50° C. and 50% humidity. The osmotic systems are dried for 1 hour at 50° C. to remove excess moisture. Attached drawing FIG. 4 shows the in vitro release rate profile for glipizide from the finished osmotic system as released in distilled water. The error bars represent the standard deviation added to and subtracted from the mean of five osmotic delivery system. An osmotic dosage form provided by the invention comprises 11 wt% glipizide, 61.50 wt% hydroxypropylcellulose of 60,000 molecular weight, 27.0 wt% polyvinylpyrrolidone of 40,000 molecular weight, 0.5%

magnesium stearate in the glipizide composition; 64.8 wt% sodium carboxymethylcellulose of 700,000 molecular weight, 29 wt% sodium chloride, 5 wt% hydroxypropylmethylcellulose of 11,200 molecular weight and 1.0 wt% ferric oxide, 0.2% magnesium stearate in the hydrogel composition; and, 93.0 wt% cellulose acetate having a 39.8% acetyl content, and 7.0 wt% polyethylene glycol having a 3350 molecular weight in the semipermeable wall formulation.

EXAMPLE 2

A dosage form adapted, designed and shaped as an osmotic drug delivery system is manufactured as follows: first, a glipizide composition is provided by blending together into a homogeneous blend 478 g of pharmaceutically acceptable polyethylene oxide comprising a 200,000 molecular weight, 66 g of glipizide and 54 g of pharmaceutically acceptable hydroxypropylmethylcellulose comprising a 11,200 molecular weight. Then, 425 ml of denatured anhydrous ethanol is added slowly with continuous mixing over 5 minutes. The freshly prepared wet granulation is screened through a 20 mesh screen dried at room temperature for 16 hours, and again screened through a 20 mesh screen. Finally, the screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for 5 minutes.

Next, a hydrogel composition is prepared as follows: first, 412.5 g of pharmaceutically acceptable polyethylene oxide comprising a 7,500,000 molecular weight, 150 g of sodium chloride and 6 g of ferric oxide separately are screened through a 40 mesh screen. Then, all the screened ingredients are mixed with 30 g of hydroxypropylmethylcellulose comprising a 11,200 molecular weight to produce a homogeneous blend. Next, 300 mg of denatured anhydrous alcohol is added slowly to the blend with continuous mixing for 5 minutes. The freshly prepared wet granulation is passed through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh screen. The screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for 5 minutes.

Next, the glipizide composition and the hydrogel composition are compressed into bilaminate tablets. First, 200 mg of the glipizide is added to a 0.375 inch (9.5 mm) punch and tamped, then, 140 mg of the hydrogel composition is added and the laminae are pressed under a pressure head of 2 tons into a contacting laminated arrangement.

Then, the bilaminate arrangements are coated with a semipermeable wall. The wall forming composition comprises 93% cellulose acetate having a 39.8% acetyl content, and 7% polyethylene glycol having a molecular weight of 3350. The wall-forming composition is dissolved in an acetone:water (90:10 wt:wt) cosolvent to make a 4% solids solution. The wall forming composition is sprayed onto and around the bilaminate in an Aeromatic® Air Suspension Coater.

Next, a 25 mil (0.635 mm) exit passageway is mechanically drilled through the semipermeable wall to connect the glipizide drug lamina with the exterior of the dosage system. The residual solvent is removed by drying for 48 hours at 50° C. and 50% humidity. Next, the osmotic systems are dried for 1 hour at 50° C. to remove excess moisture. The dosage form produced by this manufacture provides a glipizide composition comprising 11 wt% glipizide, 79.7 wt% polyethylene oxide of 200,000 molecular weight, 9 wt% hydroxypropylmethylcellulose of 11,200 molecular weight, and 0.3 wt% magnesium stearate; a hydrogel composition comprising 68.8 wt% polyethylene oxide comprising a 7,500,000 molecular weight, 25 wt% sodium chloride, 5 wt% hydroxypropylmethylcellulose, 1.0 wt% ferric oxide and 0.2 wt% magnesium stearate; and a semipermeable wall comprising 93 wt% cellulose acetate comprising a 39.8% acetyl content, and 7.0 wt% polyethylene glycol comprising a 3350 molecular weight.

Accompanying drawing FIG. 5 depicts the in vitro release rate profile of glipizide released from the final dosage form for four dosage forms. The error bars represent the standard deviation added to and subtracted from the mean of the dosage form.

DISCLOSURE OF A METHOD OF USING THE INVENTION

An embodiment of the invention pertains to a method for delivering the beneficial drug glipizide orally at a controlled rate to a warm blooded animal in need of glipizide therapy, which method comprises the steps of: (A) admitting into the warm-blooded animal a dosage form comprising: (1) a wall surrounding a compartment, the wall comprising at least in part a semipermeable polymeric composition permeable to the passage of fluid and substantially impermeable to the passage of glipizide; (2) a pharmaceutically acceptable composition in the compartment comprising about 2.5 mg to 50mg of hypoglycemic glipizide for performing an antidiabetic program; (3) a hydrogel composition in the compartment comprising a member selected from the group consisting of a polyethylene oxide having a 4,000,000 to 7,500,000 molecular weight and a sodium carboxymethylcellulose having a 200,000 to 1,000,000 molecular weight for imbibing and absorbing fluid for pushing the glipizide composition from the dosage form; and, (4) at least one passageway in the wall for releasing glipizide; (B) imbibing fluid through the semipermeable wall at a rate determined by the permeability of the semipermeable wall and the osmotic pressure gradient across the semipermeable wall causing the hydrogel composition to expand and swell; and (C) delivering the beneficial glipizide from the dosage form through the exit passage to the warm blooded animal over a prolonged period of time to produce the desired hypoglycemic effect.

In summary, it will be appreciated that the present invention contributes to the art an unexpected and unforseen dosage form that possesses the practical utility for administering aqueous insoluble glipizide from an osmotic dosage form at a dose metered release rate per unit time. While the invention has been described and pointed out in detail with reference to operative embodiments thereof it will be understood that those skilled in the art that various changes, modifications, substitutions and omissions can be made without departing from the spirit of the invention. It is intended, therefore, that the invention embrace those equivalents within the scope of the claims which follow.

We claim:

1. A pharmaceutical granulation comprising granules of 2 mg to 50 mg of substantially aqueous insoluble glipizide, from 100 mg to 320 mg of a polyethylene oxide having a 80,000 to 350,000 molecular weight, and from 5 mg to 50 mg of a hydroxypropylmethylcellulose having a 9,200 to 2,000 molecular weight, which granules are useful for manufacturing an osmotic dosage form for dispensing the glipizide for up to 22 hours

when the dosage form is in gastrointestinal tract of a patient.

2. A pharmaceutical granulation comprising granules of 2 mg to 25 mg of substantially aqueous insoluble glipizide, from 40 mg to 70 mg of a polyvinylpyrrolidone having a 30,000 to 70,000 molecular weight, and from 100 to 150 mg of a hydroxypropylcellulose having a 40,000 to 80,000 molecular weight, and wherein the granules are useful for manufacturing an osmotic dosage form for dispensing the glipizide for up to 22 hours when the dosage form is in the gastrointestinal tract of a patient.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,024,843

DATED : June 18, 1991

INVENTOR(S) : Anthony L. Kuczynski, Atul D. Ayer, Patrick S. L. Wong

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 8, line 66, "2,000" should read --22,000--.

Signed and Sealed this

Twenty-third Day of November, 1993

Attest:

Bruce Lehman

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

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International Bureau

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(54) Title: COMPOSITIONS COMPRISING MICROPARTICLES OF WATER-INSOLUBLE SUBSTANCES AND METHOD FOR PREPARING SAME

(57) Abstract

Submicron size particles of pharmaceutical or other water-insoluble or poorly water-insoluble substances are prepared using a combination of one or more surface modifiers/surfactants such as polaxomers, poloxamines, polyoxyethylene sorbitan fatty acid esters and the like together with natural or synthetic phospholipids. Particles so produced have a volume weighted mean particle size at least one-half smaller than obtainable using a phospolipid alone. Compositions so prepared are resistant to particle size growth on storage.

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COMPOSITIONS COMPRISING MICROPARTICLES OF WATER-INSOLUBLE SUBSTANCES AND METHOD FOR PREPARING SAME

This invention relates to compositions and procedures that yield sub-micron and micron stable particles of water-insoluble or poorly soluble drugs or other industrially useful insoluble compounds. The compositions of this invention include combinations of natural or synthetic phospholipds, and one or more non-ionic, anionic or cationic surfactants coated or adhered onto the surfaces of the water insoluble-compound particles. The combination of phospholipids and surfactants allows the formation and stabilization of the sub-micron and micron size compound particles via hydrophilic, lipophilic and electrostatic interactions and therefore prevent these particles from aggregation or flocculation.

BACKGROUND OF THE INVENTION

There is a critical need in the pharmaceutical and other biological based industries to formulate water-insoluble or poorly soluble substances into formulations for oral, injectable, inhalation and ophthalmic routes of delivery. Water insoluble compounds are those having poor solubility in water, that is < 5 mg/ml at physiological pH (6.5-7.4). Preferably their water solubility is $<$ 1 mg/ml, more preferably < 0.1 mg/ml. It is desirable that the drug is stable in water as a dispersion; otherwise a lyophilized or spray-dried solid form may be desirable.

As used herein, "micro" refers to a particle having diameter of from nanometers to micrometers. Microparticles, as used herein, refer to solid particles of irregular, non-spherical or spherical shapes. Formulations containing these microparticles provide some specific advantages over the unformulated non-micronized drug particles, which include improved oral bioavailability of drugs that are poorly absorbed from GI tract, development of injectable formulations that are currently available only in oral dosage form, less toxic injectable formulations that are currently prepared with organic solvents, sustained release of intramuscular injectable drugs that are currently administered through daily injection or constant infusion. and preparation of inhaled, ophthalmic formulation of drugs that otherwise could not be formulated for nasal or ocular use.

Current technology for delivering insoluble drugs as described in US Patents 5,091,188; 5,091,187 and 4,725,442 focuses on (a) either coating small drug particles with natural or synthetic phospholipds or (b) dissolving the drug in a suitable lipophilic carrier and forming an emulsion stabilized with natural or semisynthetic phospholipids. One of the disadvantages of these formulations is that certain drug particles in suspension tend to grow over time because of the dissolution and reprecipitation phenomenon known as the "Oswald ripening".

DESCRIPTION OF THE INVENTION

The present invention focuses on preparing submicron size particles using a combination of surface modifier(s) with a phospholipid, and how the growth of particle size, and hence storage stability, is

controlled by adding a combination of surface modifier(s) with a phospholipid to the formulation.

The use of a surface modifier or combination of surface modifiers in addition to a phospholipid is characterized by its ability to result in volume weighted mean particle size values that are (i) at least 50% and preferably about 50-90% smaller than what can be achieved using phospholipid alone without the use of a surfactant with the same energy input, and (ii) provide compositions resistant to particle size growth on storage. While resistance to particle size growth on storage was an objective of this invention we were surprised to observe a significant reduction in particle size with the addition of the surfactant. In order to achieve the advantages of the present invention it is necessary that the phospholipid and the surfactant both be present at the time of particle size reduction or precipitation.

Although we do not wish to be bound by any particular theory, it appears that these surface modifiers generally, that is phospholipids and one or more surfactants, adsorb to the surfaces of drug particles. and (a) convert lipophilic to hydrophilic surfaces with increased steric hindrance/stability, and (b) possibly modify zeta potential of surfaces with more charge repulsion stabilization. The concentrations of surface modifiers used in the process described here are normally above their critical micelle concentrations (CMC) and hence facilitate the formation of sub-micron particles by stabilizing the particles.

Phospholipid and surface modifier(s) are adsorbed on to the surfaces of drug particles in sufficient quantity to retard drug particle growth, reduce drug average particle size from 5 to 100 μm to sub-micron and micron size particles by one or combination of methods known in the art, such as sonication, homogenization, milling, microfluidization, precipitation or recrystallization or precipitation from supercritical fluid, and maintain sub-micron and micron size particles on subsequent storage as suspension or solid dosage form.

The concentration of phospholipid or surface modifier in the suspension or solid dosage form can be present in the range of 0.1 to 50%, preferably 0.2 to 20%, and more preferably 0.5 to 10%.

The formulations prepared by this invention may be lyophilized into powders, which can be resuspended or filled into capsules or converted into granules or tablets with the addition of binders and other excipients known in the art of tablet making.

By industrially useful insoluble or poorly soluble compounds we include biologically useful compounds, imaging agents, pharmaceutically useful compounds and in particular drugs for human and veterinary medicine. Water insoluble compounds are those having a poor solubility in water, that is less than 5 mg/ml at a physiological pH of 6.5 to 7.4, although the water solubility may be less than 1 mg/ml and even less than 0.1 mg/ml.

Examples of some preferred water-insoluble drugs include immunosuppressive and immunoactive agents, antiviral and

antifungal agents, antineoplastic agents, analgesic and anti-inflammatory agents, antibiotics, anti-epileptics, anesthetics, hypnotics, sedatives, antipsychotic agents, neuroleptic agents, antidepressants, anxiolytics, anticonvulsant agents, antagonists, neuron blocking agents, anticholinergic and cholinomimetic agents, antimuscarinic and muscarinic agents, antiadrenergic and antarrhythmics, antihypertensive agents, antineoplastic agents, hormones, and nutrients. A detailed description of these and other suitable drugs may be found in *Remington's Pharmaceutical Sciences*, 18th edition, 1990, Mack Publishing Co. Philadelphia, PA.

The phospholipid may be any natural or synthetic phospholipid, for example phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, lysophospholipids, egg or soybean phospholipid or a combination thereof. The phospholipid may be salted or desalted, hydrogenated or partially hydrogenated or natural semisynthetic or synthetic.

Examples of some suitable second surface modifiers include: (a) natural surfactants such as casein, gelatin, tragacanth, waxes, enteric resins, paraffin, acacia, gelatin, cholesterol esters and triglycerides, (b) nonionic surfactants such as polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline

cellulose, polyvinyl alcohol, polyvinylpyrrolidone, and synthetic phospholipids, (c) anionic surfactants such as potassium laurate, triethanolamine stearate, sodium lauryl sulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, negatively charged phospholipids (phosphatidyl glycerol, phosphatidyl inosite, phosphatidylserine, phosphatidic acid and their salts), and negatively charged glyceryl esters, sodium carboxymethylcellulose, and calcium carboxymethylcellulose, (d) cationic surfactants such as quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, chitosans and lauryldimethylbenzylammonium chloride, (e) colloidal clays such as bentonite and veegum. A detailed description of these surfactants may be found in Remington's Pharmaceutical Sciences, and Theory and Practice of Industrial Pharmacy, Lachman et al, 1986.

More specifically, examples of suitable second surface modifiers include one or combination of the following: polaxomers, such as Pluronic™ F68, F108 and F127, which are block copolymers of ethylene oxide and propylene oxide available from BASF, and poloxamines, such as Tetronic™ 908 (T908), which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylene-diamine available from BASF, Triton™ X-200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas. Tween 20, 40, 60 and 80, which are polyoxyethylene sorbitan fatty acid esters, available from ICI Speciality Chemicals, Carbowax™ 3550 and 934, which are polyethylene glycols available from Union Carbide, hydroxy propylmethylcellulose, dimyristoyl phosphatidylglycerol sodium salt,

sodium dodecylsulfate, sodium deoxycholate. and cetyltrimethylammonium bromide.

It is thought that some of the functions of the second surface modifier(s) as it relates to this invention are suppressing the process of Oswald Ripening and therefore maintaining the particle size, increasing the storage stability, minimizing sedimentation. and decreasing the particle growth during lyophilization and reconstitution; adhere or coat firmly onto the surfaces of water-insoluble drug particles and therefore modify the interfaces between the particles and the liquid in the resulting formulations; increase the interface compatibility between water-insoluble drug particles and the liquid; and possibly to orient preferentially themselves with the hydrophilic portion sticking into the aqueous solution and the lipophilic portion strongly adsorbed at the water-insoluble drug particle surfaces

Considerable variations as to the identities and types of phospholipid and especially the surface active agent or agents should be expected depending upon the drug or active agent selected as the surface properties of these small particles are different. The most advantageous surface active agent for the insoluble drug will be apparent following empirical tests to identify the surfactant or surfactant system/combination resulting in the requisite particle size and particle size stability on storage over time.

Various procedures can be used to produce these stable sub-micron and micron size particles including mixing the insoluble

substance with phospholipid and precipitating from a dissolved mixture of the substance, phospholipid and surfactant using other surfactants followed by sonication, milling, homogenization, microfluidization, and antisolvent and solvent precipitation. Mannitol and other agents may be added to adjust the final formulation to isotonicity as well as a stabilizing aid during drying.

Unless otherwise specified, all parts and percentages reported herein are weight per unit volume (w/v), in which the volume in the denominator represents the total volume of the system. Diameters of dimensions are given in millimeters (mm = 10^{-3} meters), micrometers (µm = 10^{-6} meters), nanometers (nm = 10^{-9} meters) or Angstrom units (= 0.1 nm). Volumes are given in liters (L), milliliters (mL = 10^{-3} L) and microliters (µL = 10^{-6}L). Dilutions are by volume. All temperatures are reported in degrees Celsius. The compositions of the invention can comprise, consist essentially of or consist of the materials set forth and the process or method can comprise, consist essentially of or consist of the steps set forth with such materials.

The following examples further explain and illustrate the invention:

Example 1

Microparticle-cyclosporine, of an immunosuppressive drug, was prepared as follows. The composition and concentration of excipients of the microparticle cyclosporine formulation are listed below:

Cyclosporine	50 mg/ml
Egg Phosphatidylcholine	100 mg/ml
Mannitol	55 mg/ml
Tween 80	10 mg/ml
Distilled Water	qs to 100%
Total Volume	20 ml

Cyclosporine with an average particle size from 5-100 μm, and mannitol were purchased from Sigma, egg phosphatidylcholine was produced by Pfanstiehl, Tween 80 was purchased from ICI.

The above components were placed in a 30 ml beaker and pre-mixed with a hand-held biohomogenizer (Honeywell DR 4200 model GP) for 1-5 min. During homogenization, dilute NaOH was added to the pre-mix to adjust the pH from 3.1 to 7 ± 0.5. The pre-mix was placed in a water jacketed vessel (50 ml capacity) through which thermostated water at 4°C was circulated to control the temperature of the formulation. The pre-mix was subjected to high shear energy of a probe sonicator (Fisher, model 550 Sonic Dismembrator) with a 0.5 inch diameter probe. Sonic pulses of 10 seconds at 10-seconds intervals at a power setting of 5 were utilized. During sonication the temperature of the formulation was 18 ± 2°C. The pH during sonication was adjusted to 7 ± 0.5 with dilute NaOH. Total sonication time employed to prepare the microparticle cyclosporine was usually 10.5 hours or less. The microparticle-cyclosporine formulation was placed in 20 ml vials and stored at 4 and 25°C for further stability studies.

Particle size distribution of the suspension was analyzed with a NICOMP model 370 Particle Size Analyzer. This instrument utilizes photon correlation spectroscopy for particle sizing in the submicron region. A small volume of the suspension was diluted with water and placed in the cell of the particle size analyzer. Particle size determination based on volume weighted and number weighted particle size determination of the suspension, represented as a Gaussian distribution by the NICOMP 370 software, yielded the mean particle size values, which are listed below in Table I.

Table I: Volume-and Number-weighted Particle Size Stability of Microparticle-Cyclosporine

Storage Time	Storage at 4°C Mean Particle Size (nm)		Storage at 25°C Mean Particle Size (nm)	
Days	Volume-Weighted	Number-Weighted	Volume-Weighted	Number-Weighted
0	361	63	361	63
7	337	69	423	67
51	358	76	455	66

Approximately 20 µl of the freshly prepared suspension was placed on a clean slide, with a clean cover glass, and examined under an Olympus BH2 microscope with 1000X magnification. An eye-piece equipped with a graticule was used to estimate the particle size. Most of the particles in the suspension were 0.3-0.5 µm.

Furthermore, microscopic examination of the suspension confirmed non-agglomerated or flocculated micron and sub-micron size drug particles exhibiting Brownian motion.

Example 2

For purpose of comparison (not according to the invention) using only a phospholipid, microparticle-cyclosporine with lecithin alone (without the second surface modifier. Tween 80) was also prepared using the same procedure as Example 1. The suspension was stored in 20 ml glass vials for storage stability studies. The volume and number weighted mean particle size values of the suspension stored at 4 and 25°C are listed below. The results in Table II illustrate that the presence of lecithin alone (without the presence of Tween 80) does not provide the particle size reduction and enhancement in storage stability as described in Example 1.

Table II: Volume-weighted Particle Size Stability of Microparticle-Cyclosporine

Storage Time	Storage at 4°C Mean Particle Size (nm)		Storage at 25°C Mean Particle Size (nm)	
Days	Volume-Weighted	Number-Weighted	Volume-Weighted	Number-Weighted
0	704	91	704	91
1	1472	503	2230	755
6	1740	416	2290	874

Example 3

For purpose of comparison (not according to the invention) using only a surface modifier, microparticle-cyclosporine with Tween 80 alone (without a phospholipid, egg phosphatidylcholine) was also prepared using the same procedure as Example 1. The suspension was stored in 20 ml glass vials. The results in Table III illustrate that the presence of Tween 80 alone (without the presence of phospholipid does not provide particle size reduction as in Example 1.

Table III: Volume- and Number-weighted Particle Size Stability of Microparticle-Cyclosporine

Mean Particle Size (nm)		
Day	Volume-Weighted	Number-Weighted
0	521	67

Example 4

The following microparticle-Docosanol formulations were prepared by the process of the invention with Tween 80, Tween 20, egg phosphatidylcholine, and/or Phospholipon 90H as surface modifiers. Docosanol is available from Sigma. The formulations were prepared according to the procedures of Example 1. The compositions and concentration of excipients of the microparticle formulations are listed below:

Microparticle-Docosanol (Example 4.1, comparative)

Docosanol	20 mg/ml
Egg Phosphatidylcholine	50 mg/ml
Mannitol	55 mg/ml
Distilled Water	qs to 100%
Total Volume	20 ml

Microparticle-Docosanol (Example 4.2)

Docosanol	20 mg/ml
Egg Phosphatidylcholine	50 mg/ml
Mannitol	55 mg/ml
Tween 80	10 mg/ml
Distilled Water	qs to 100%
Total Volume	20 ml

Microparticle-Docosanol (Example 4.3)

Docosanol	20 mg/ml
Egg Phosphatidylcholine	50 mg/ml
Mannitol	55 mg/ml
Tween 20	10 mg/ml
Distilled Water	qs to 100%
Total Volume	20 ml

Microparticle-Docosanol (Example 4.4)

Docosanol	20 mg/ml
Phospholipon 90H	30 mg/ml
Mannitol	55 mg/ml
Tween 80	10 mg/ml
Distilled Water	qs to 100%
Total Volume	20 ml

Microparticle-Docosanol (Example 4.5, Comparative)

Docosanol	20 mg/ml
Mannitol	55 mg/ml
Tween 80	10 mg/ml
Distilled Water	qs to 100%
Total Volume	20 ml

The mean volume-and number-weighted particle size values of the suspension were 286 nm, and 98 nm, respectively.

The volume weighted mean particle size values of the above suspension stored at 4°C are listed below in Table IV.

Table IV: Volume-weighted and Number Weighted Particle Size Stability of Microparticle-Docosanol Stored at 4°C.

Storage Time	(Example 4.1) Mean Particle Size (nm)		(Example 4.2) Mean Particle Size (nm)	
Days	Volume-Weighted	Number-Weighted	Volume-Weighted	Number-Weighted
0	688	--	112	55
30	ND	ND	156	81

Storage Time	(Example 4.3) Mean Particle Size (nm)		(Example 4.4) Mean Particle Size (nm)	
Days	Volume-Weighted	Number-Weighted	Volume-Weighted	Number-Weighted
0	129	61	90	35
30	184	99	127	39

ND = Not Determined

The above data illustrate the much smaller particles produced by the present invention with the presence of a surfactant in addition to the phospholipid and that these particles retain their particle size over time without significant increase in size.

Example 5

The following seven microparticle-RTP-4055 (an antiviral drug) formulations were prepared with combinations of Tween 80, Tetronic 908, Pluronic F-68, egg phosphatidylcholine, and/or phospholipon 90H as surface modifiers. The details of the sonication method are similar to those discussed in Example 1. The compositions and concentration of excipients of the microparticle formulations are listed below:

Microparticle-RTP-4055 (Example 5.1, Comparative)

RTP-4055	50 mg/ml
Egg Phosphatidylcholine	50 mg/ml
Distilled Water	qs to 100%
Total Volume	25 ml

The mean volume weighted particle size of the suspension was 3195 nm.

Microparticle-RTP-4055 (Example 5.2)

RTP-4055	50 mg/ml
Egg Phosphatidylcholine	50 mg/ml
Mannitol	55 mg/ml
Pluronic F-68	5 mg/ml
Distilled Water	qs to 100%
Total Volume	25 ml

The mean volume- and number-weighted particle size values of the suspension were 672 nm and 76 nm respectively.

Microparticle-RTP-4055 (Example 5.3)

RTP-4055	50 mg/ml
Egg Phosphatidylcholine	50 mg/ml
Mannitol	55 mg/ml
Tetronic 908	5 mg/ml
Distilled Water	qs to 100%
Total Volume	25 ml

The mean volume- and number- weighted particle size values of the suspension were 436 nm and 59 nm respectively.

Microparticle-RTP-4055 (Example 5.4, Comparative)

RTP-4055	50 mg/ml
Phospholipon 90H	30 mg/ml
Distilled Water	qs to 100%
Total Volume	25 ml

The mean volume- number- weighted particle size values of the suspension were 1117 nm. and 108 nm respectively.

Microparticle-RTP-4055 (Example 5.5)

RTP-4055	50 mg/ml
Phospholipon 90H	30 mg/ml
Mannitol	55 mg/ml
Dimyristoylphosphatidyl choline (DMPG)	3 mg/ml
Tween 80	10 mg/ml
Distilled Water	qs to 100%
Total Volume	25 ml

The mean volume weighted particle size of the suspension was 236 nm. The particle size of the suspension stored at 4°C for 1 week and 1 month are 328 and 397 nm, respectively, which indicates the stability of the suspension.

Microparticle-RTP-4055 (Example 5.6)

RTP-4055	50 mg/ml
Phospholipon 90H	30 mg/ml
Mannitol	55 mg/ml
Tween 80	10 mg/ml
Distilled Water	qs to 100%
Total Volume	25 ml

The mean volume- and number- weighted particle size values of the suspension were 382 nm and 59 nm respectively. Within the

error limits, there was no variation in the mean particle size after one week of storage at 4°C.

Microparticle-RTP-4055 (Example 5.7, Comparative)

RTP-4055	50 mg/ml
Mannitol	55 mg/ml
Tween 80	10 mg/ml
Distilled Water	qs to 100%
Total Volume	25 ml

The volume- and number-weighted mean particle size values of the suspension were 545 nm, and 75 nm, respectively within the error limits, there was no variation in the mean particle size after one week of storage at 4°C.

Example 6

The following six microparticle-Piroxicam formulations were prepared with combination of Tween 80, Tetronic 908, Pluronic F-68, and/or egg phosphatidylcholine as surface modifiers. Piroxicam was received from Cipla. The details of the sonication method are similar to those discussed in example 1. The compositions and concentration of excipients of the microparticle formulations are listed below:

Microparticle-Piroxicam (Example 6.1)

Piroxicam	67 mg/ml
Egg Phosphatidylcholine	67 mg/ml
Mannitol	67 mg/ml
Tween 80	5 mg/ml
Tetronic 908	5 mg/ml
Distilled Water	qs to 100% (w/v)
Total Volume	15 ml

The mean volume- and number- weighted particle size values of the suspension were 674 nm and 72 nm respectively.

Microparticle-Piroxicam (Example 6.2)

Piroxicam	67 mg/ml
Egg Phosphatidylcholine	67 mg/ml
Mannitol	67 mg/ml
Tetronic 908	5 mg/ml
Distilled Water	qs to 100% (w/v)
Total Volume	15 ml

The mean volume- and number- weighted particle size values of the suspension were 455 nm and 58 nm respectively.

Microparticle-Piroxicam (Example 6.3)

Piroxicam	67 mg/ml
Egg Phosphatidylcholine	67 mg/ml
Mannitol	67 mg/ml
Pluronic F-68	5 mg/ml
Distilled Water	qs to 100% (w/v)
Total Volume	15 ml

The mean volume- and number- weighted particle size values of the suspension were 564 nm and 68 nm respectively.

Microparticle-Piroxicam (Example 6.4)

Piroxicam	67 mg/ml
Egg Phosphatidylcholine	67 mg/ml
Mannitol	67 mg/ml
Tween 80	5 mg/ml
Cetyltrimethylammonium bromide	10 mg/ml
Distilled Water	qs to 100% (w/v)
Total Volume	15 ml

The mean volume- and number- weighted particle size values of the suspension were 479 nm and 80 nm respectively.

Microparticle-Piroxicam (Example 6.5)

Piroxicam	67 mg/ml
Egg Phosphatidylcholine	67 mg/ml
Mannitol	67 mg/ml
Cetyltrimethylammonium bromide	10 mg/ml
Distilled Water	qs to 100% (w/v)
Total Volume	15 ml

The mean volume- and number- weighted particle size values of the suspension were 670 nm and 128 nm respectively.

Microparticle-Piroxicam (Example 6.6, Comparative)

Piroxicam	67 mg/ml
Mannitol	67 mg/ml
Tween 80	5 mg/ml
Tetronic 908	5 mg/ml
Distilled Water	qs to 100%
Total Volume	25 ml

The volume- and number- weighted particle size values of the suspension were 1184 nm and 385 nm, respectively.

WHAT IS CLAIMED IS:

1. A composition of microparticles of a water-insoluble substance comprising particles of an industrially useful water-insoluble or poorly soluble compound, a phospholipid and at least one non-ionic, anionic or cationic surfactant, in which the surfactant or surfactants provide volume-weighted mean particle size values of the water-insoluble compound at least 50% smaller than particles produced without the presence of the surfactant using the same energy input.

2. A pharmaceutical composition of microparticles of a water-insoluble substance comprising particles of an industrially useful water-insoluble or poorly soluble compound, a phospholipid and at least one non-ionic, anionic or cationic surfactant, in which the surfactant or surfactants provide volume-weighted mean particle size values of the water-insoluble compound at least 50% smaller than particles produced without the presence of the surfactant using the same energy input.

3. The pharmaceutical composition of claim 2 for oral, inhalation, ocular, nasal or injectable administration.

4. The pharmaceutical composition of claim 3 in injectable form for intravenous, intra-arterial, intra-muscular, intradermal, subcutaneous, intra-articular, cerebrospinal, epidural, intracostal, intraperitoneal, intratumor, intrabladder, intra-lesion or subconjunctival administration.

5. A dried suspension of the composition of claim 4 which can be resuspended in aqueous or non-aqueous media.

6. A suspension, spray-dried powder, lyophilized powder granules or tablets of the composition of claim 2.

7. A composition of claim 1 in which the water-insoluble compound is a biologically useful compound or an imaging agent.

8. The composition of claim 1 or claim 2 wherein the surfactant is a polyoxyethylene sorbitan fatty acid ester, a block copolymer of ethylene oxide and propylene oxide, a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine, an alkyl aryl polyether sulfonate, polyethylene glycol, hydroxy propylmethylcellulose, sodium dodecylsulfate, sodium deoxycholate, cetyltrimethylammonium bromide or combinations thereof.

9. The process of claim 1 or 2 wherein the phospholipid is of egg or plant origin or semisynthetic or synthetic in partly or fully hydrogenated form or in a desalted or salt form such as phosphatidylcholine, phospholipon 90H or dimyristoyl phosphatidylglyerol sodium salt, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, lysophospholipids or combinations thereof.

10. A process for preparing sub-micron and micron sized, stable particles of water-insoluble or a poorly soluble industrially useful compound using natural or synthetic phospholipids, said process comprising reducing the particle size by sonication, homogenization, milling, microfluidization and precipitation, or recrystallization and precipitation of the compound using antisolvent and solvent precipitation including from supercritical fluids in the presence of a phospholipid and at least one non-ionic. anionic or cationic surfactant.

11. A process of preparing microparticles of a water-insoluble or poorly soluble compound comprising the steps of:

(1) mixing particles of a water-insoluble or poorly soluble industrially useful compound with a phospholipid and at least one non-ionic, anionic or cationic surfactant, and thereafter

(2) applying energy to the mixture sufficient to produce volume-weighted mean particle size values of the compound at least 50% smaller than particles produced without the presence of the surfactant using the same energy input.

12. The process of claim 10 or 11 wherein the phospholipid is of egg or plant origin or semisynthetic or synthetic in partly or fully hydrogenated form or in a desalted or salt form such as phosphatidylcholine, phospholipon 90H or dimyristoyl phosphatidylglyerol sodium, salt, phosphatidylethanolamine, phosphatidiylserine, phosphatidic acid, lysophospholipids, or combinations thereof.

13. The process of claim 10 or 11 wherein the surfactant is a polyoxyethylene sorbitan fatty acid ester, a block copolymer of ethylene oxide and propylene oxide, a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine, an alkyl aryl polyether sulfonate, polyethylene glycol, hydroxy propylmethylcellulose, sodium dodecylsulfate, sodium deoxycholate, cetyltrimethylammonium bromide or combinations thereof.

14. The process of claim 10 or 11 wherein the surfactant is present above the critical micelle concentration.

15. The process of claim 10 or 11 in which the compound is a biologically useful compound or an imaging agent.

16. A composition comprising microparticles prepared by the process of claim 10.

17. A composition comprising microparticles produced by the process of claim 11.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/04695

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/51 A61K9/14 A61K49/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 601 618 A (STERLING WINTHROP INC) 15 June 1994 see the whole document ---	1-4, 6-13, 15-17
X	EP 0 602 700 A (STERLING WINTHROP INC) 22 June 1994 see the whole document ---	1-4,6-9
X	US 5 447 710 A (NA GEORGE C ET AL) 5 September 1995 see the whole document ---	1-4,6-9
X	US 5 326 552 A (NA GEORGE C ET AL) 5 July 1994 see the whole document --- -/--	1-4,6-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
2 December 1997	15/12/1997

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/04695

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